Gestione del follow-up a lungo termine del paziente trattato con CAR-T

GIORNATE EMATOLOGICHE VICENTINE 2025

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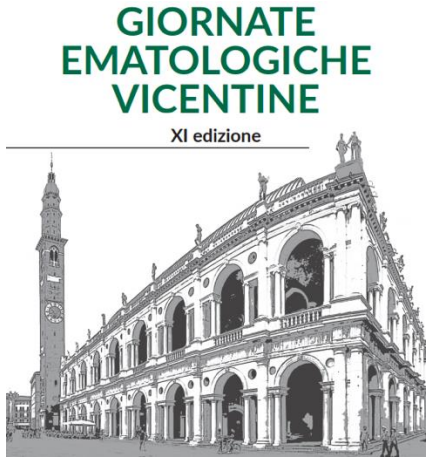


Background

- CAR-T are expanding: lymphoid malignancies, autoimmune diseases, solid tumors
- Early post-infusion care -> **standardized** (CRS and ICANS management, scores, algorithms…)

- Long-term follow-up still not clearly defined

Different aspects seem crucial

- **Logisitcs**: Coordination between CAR-T centers & referring hospitals
- **Disease-specific monitoring**: relapses, even late failures
- **Other toxicities** (cytopenias, cardiac toxicities)
- **Infection** prevention & management
- Second **cancers**
  - Management of NRM
- Psychosocial, social & economic aspects
- Fertility

Logistics of Follow-Up

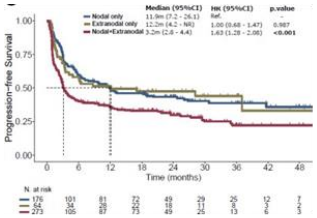
Different among countries, centres…

- First 3 months: ideally by qualified CAR-T center
- After 3 months: discuss shared care with trained centers
- Follow-up required up to 15 years
- Protocols differ by lymphoma, myeloma, ALL

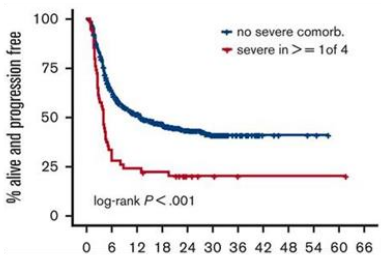
Hematological Monitoring

- Disease-specific surveillance

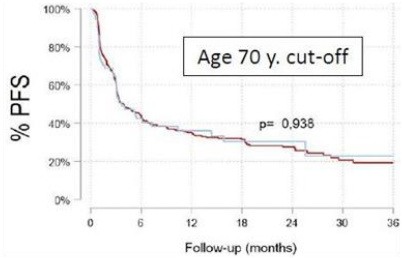
Risk factors identified



Extranodal involvement

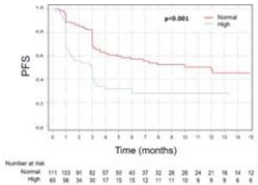


Comorbidities

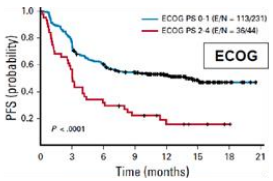


Age has no significant impact

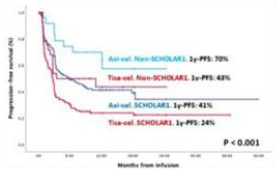
3L+ Real world evidence



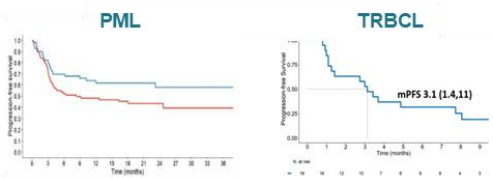
High LDH



ECOG-PS



SCHOLAR-1 criteria

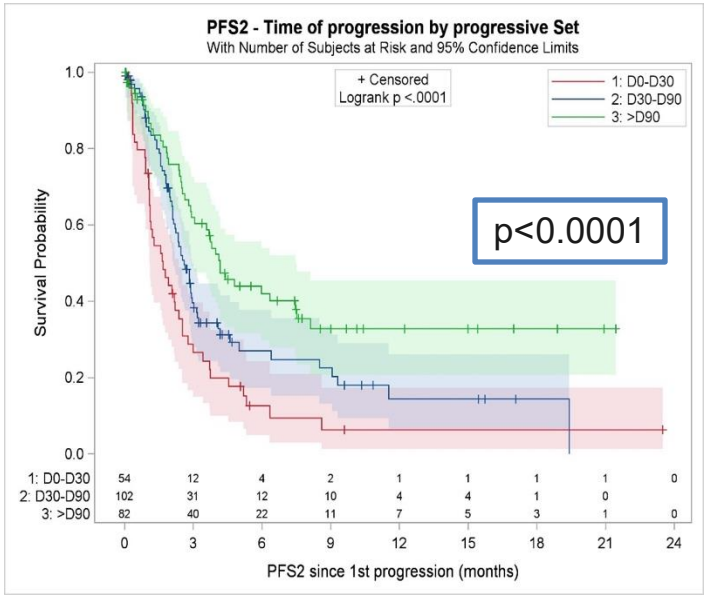


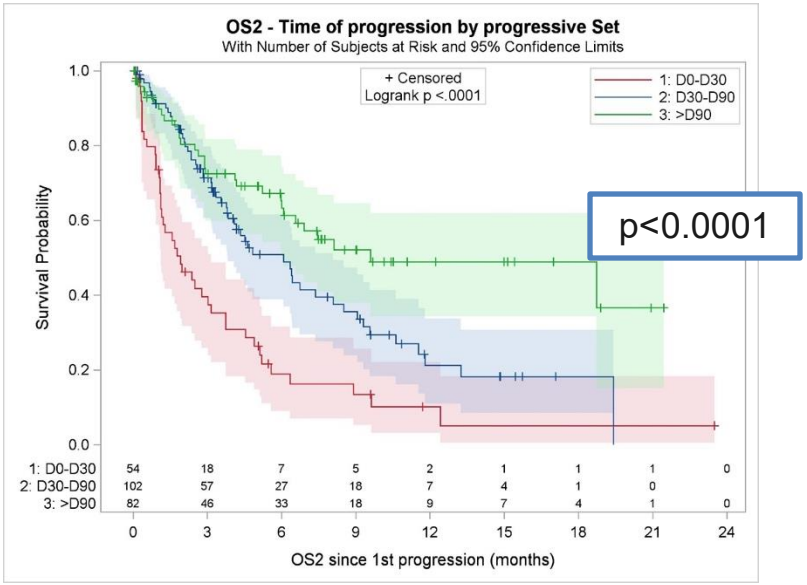
Histologies: Best PML/ Worst TRBCL

PML Primary mediastinal lymphoma, TRBCL T rich B cell lymphoma

Iacoboni et al, Hematologica 2025, Kwon M et al Hematologica 2022, Nastoupil L et al, JCO 2020, Bailen et al TCT 2024, Bastos-Oreiro et al TCT 2023; ShouseG et al, Blood Adv 2023,, ChiappellaA et al; Leukemia 2024, Bastos-Oreiro and Iaconobi et al, Hemasphere 2024

Survivals of patients at failure after CAR T-cells for DLBCL





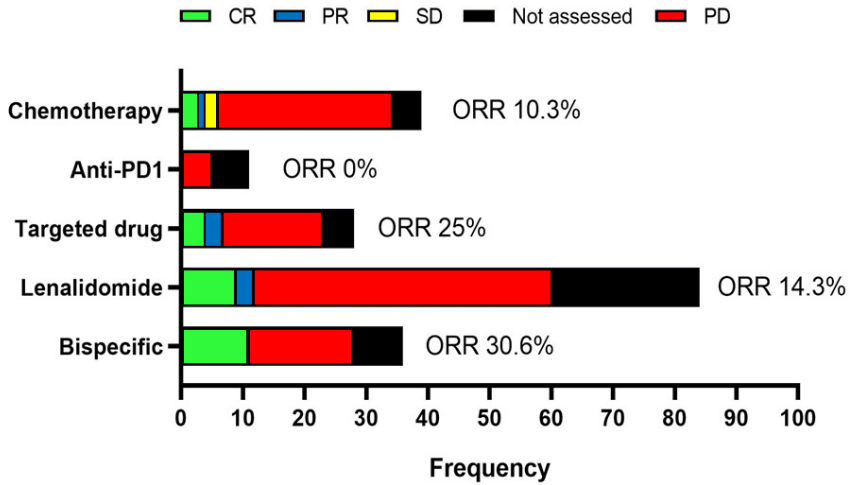
- **D0-30: 1.7 months (95%CI, 1.1-2.4)**
- **D30-90: 2.6 months (95% CI, 2.1-3.0)**
- **> D90: 4.2 months (95%CI, 2.9-7.5)**

- **D0-30: 1.9 months (95% CI, 1.1-3.2)**
- **D30-90: 6.1 months (95% CI, 3.8-8.1)**
- **D>90: 9.6 months (95%CI, 6.0 – Not reached)**

R Di Blasi et al, Blood 2022

CARLATE: late failures after CAR T-cell treatment

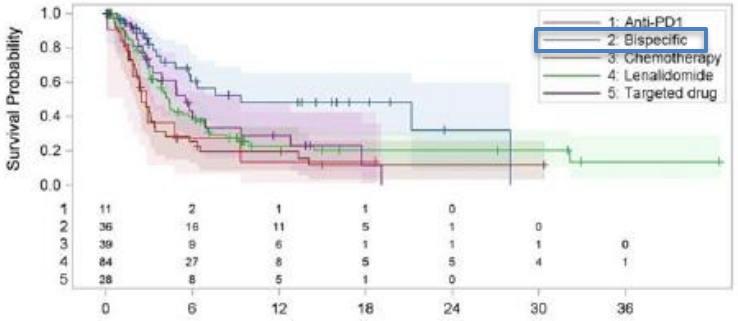
- Nationwide, real-world, registry-based study (DESCAR-T, France). July 2018 – March 2024
- 747 (49%) relapsed → **298 (39.9%)** were late failures (>3 months post-infusion)
- Median age: 62 years; 69% DLBCL subtype.

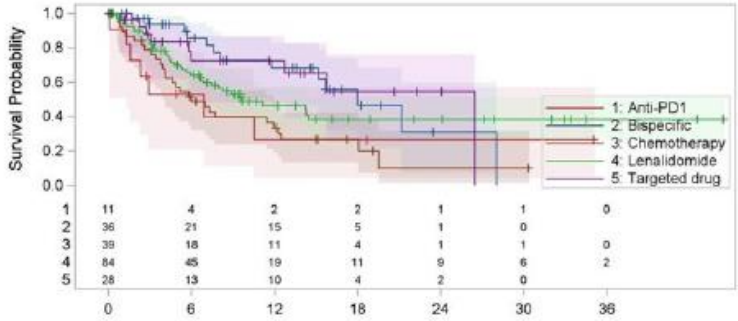


F Erbella et al, Blood Advances 2025, In press

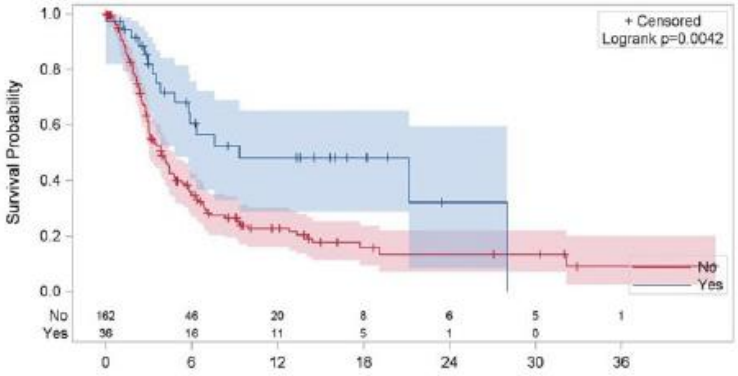
CARLATE: late failures after CAR T-cell treatment

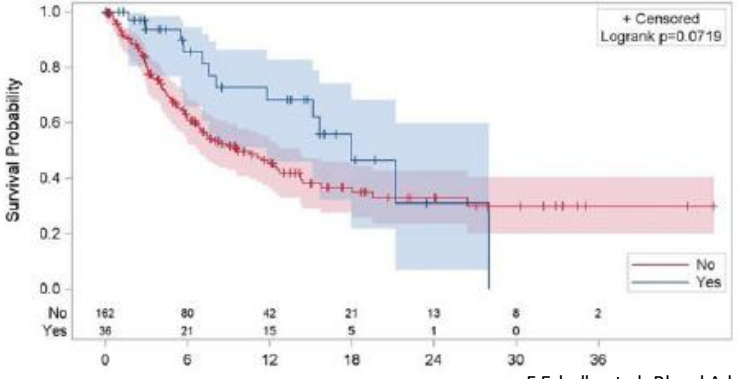
A **PFS-2 and OS-2 of late failure population according to treatment group**





C **PFS-2 and OS-2 of patients treated with bsAsb vs other therapies**





F Erbella et al, Blood Advances 2025, In press

Prognostic factors in L2

Retrospective single-center study (Saint-Louis University Hospital, Paris)
59 patients with R/R 2L LBCL treated with second-line axi-cel or liso-cel (2022–2024).

Efficacy: 3-month CAR T-cell failure occurred in **30.5%** of patients. Six-month **EFS** was **58.9%** and **OS 84.5%**. Outcomes were similar for axi-cel and liso-cel.

Toxicity: Cytokine release syndrome (CRS) was more frequent and severe with axi-cel, leading to more ICU transfers.

Vély A et al, please do not share, manuscript ongoing

Prognostic factors in L2

Outcome	Independent Predictors
3-month CAR T-cell failure	Progressive disease (PD) at infusion, ferritin ≥400 µg/L, high BMI
Event-free survival (EFS)	High BMI, ECOG PS ≥2, total metabolic tumor volume (TMTV) >80 mL
Overall survival (OS)	Age ≥75 years, high BMI, ECOG PS ≥2

- Elevated **CRP** and **LDH** correlated with worse outcomes (univariable).
- **Low effector-to-target (E:T) ratio** (CAR T expansion normalized by tumor volume) strongly predicted treatment failure and poor EFS.

- Most failures occurred within the first three months post-infusion, emphasizing the importance of **early tumor control** and **patient selection**.
- **BMI's negative impact** on outcomes contrasts with some prior reports, suggesting complex metabolic influences on CAR T-cell function.

Vély A et al, please do not share, manuscript ongoing

(Persistent) Cytopenias: ICAHT

Bi-phasic
-1st lymphodepletion
-2nd immuno-modulated
(similar to post Rituximab neutropenia)

Fried et al. Bone Marrow Transplant. 2019

Up to 38% treated pts
- Thrombocytopenia and LD
- Early CRS

Nahas et al. Leukemia and Lymphoma 2019

Non B cytopenia:
30% at M1, 10% at 1 y (axi-cel)

Logue et al. Haematologica 2020

Baseline Features	0 Point	1 Point	2 Points
Platelet Count	> 175,000/µl	75,000 – 175,000/µl	< 75,000/µl
Absolute Neutrophil Count (ANC)	> 1200/µl	< 1200/µl	-
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

Bone marrow (PLT, Hb, ANC) + inflammation (ferritine, CRP), and tumoral micro-environnement

After day 21, grade ≥3 cytopenia:

neutropenia 30%-38%,
thrombocytopenia 21%-29%
anemia 5% -17%

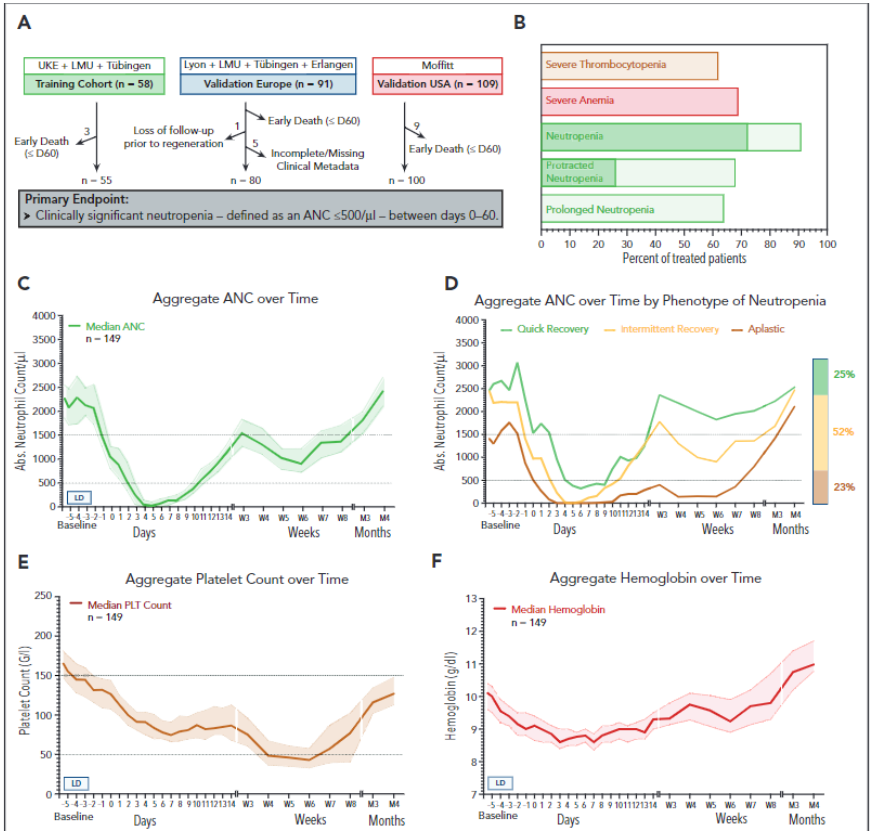
Rejeski et al. Blood 2021

HT and ICAHT

235 pts:

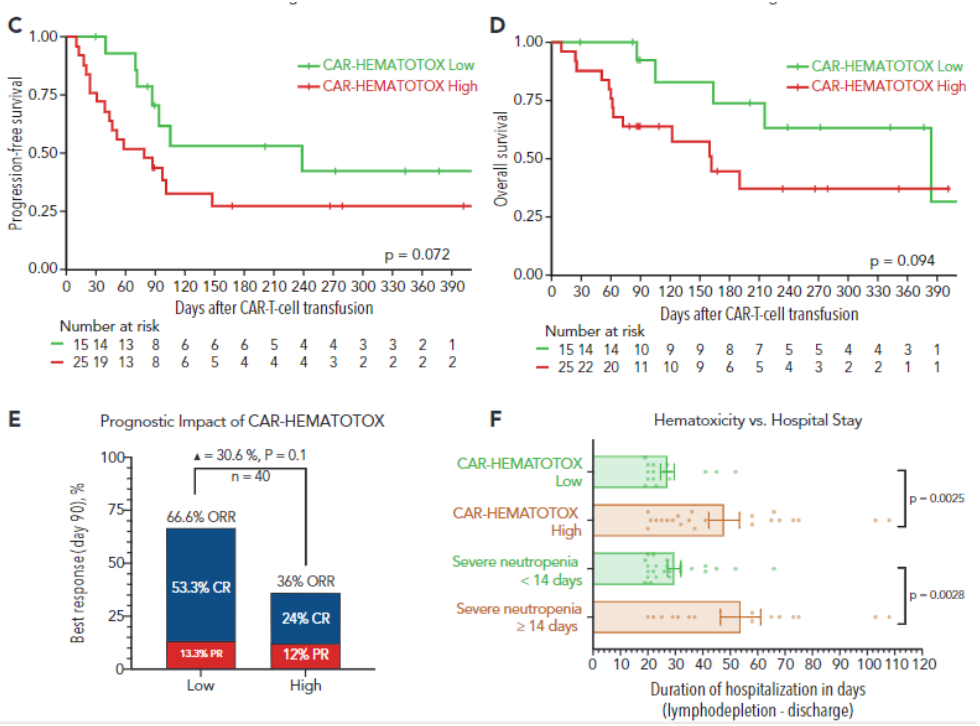
- End point: neutropenia grade IV at D60
- **≥3 neutropenia 91%, anemia 69%, thrombocytopenia 62%**
- Median **duration** of severe neutropenia (ANC ,500 cells per mL) was **9 days** (95%confidence interval [CI], 8-10 days)
- No difference by CAR T-cell product

- A **biphasic temporal course with intermittent recovery** represents the dominant phenotype of neutrophil recovery after CAR T-cell therapy



Rejeski et al. Blood 2021

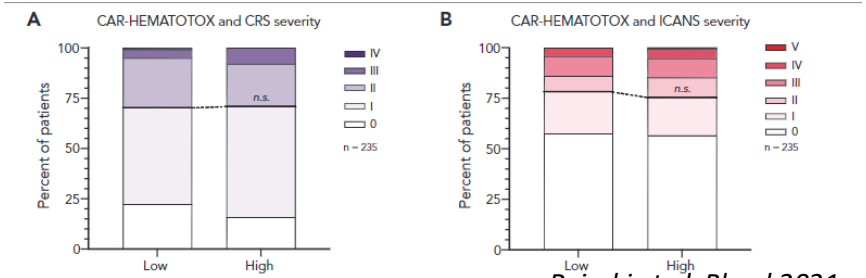
HT impact on survival



High CAR-HEMATOTOX (Before CAR T-cells)

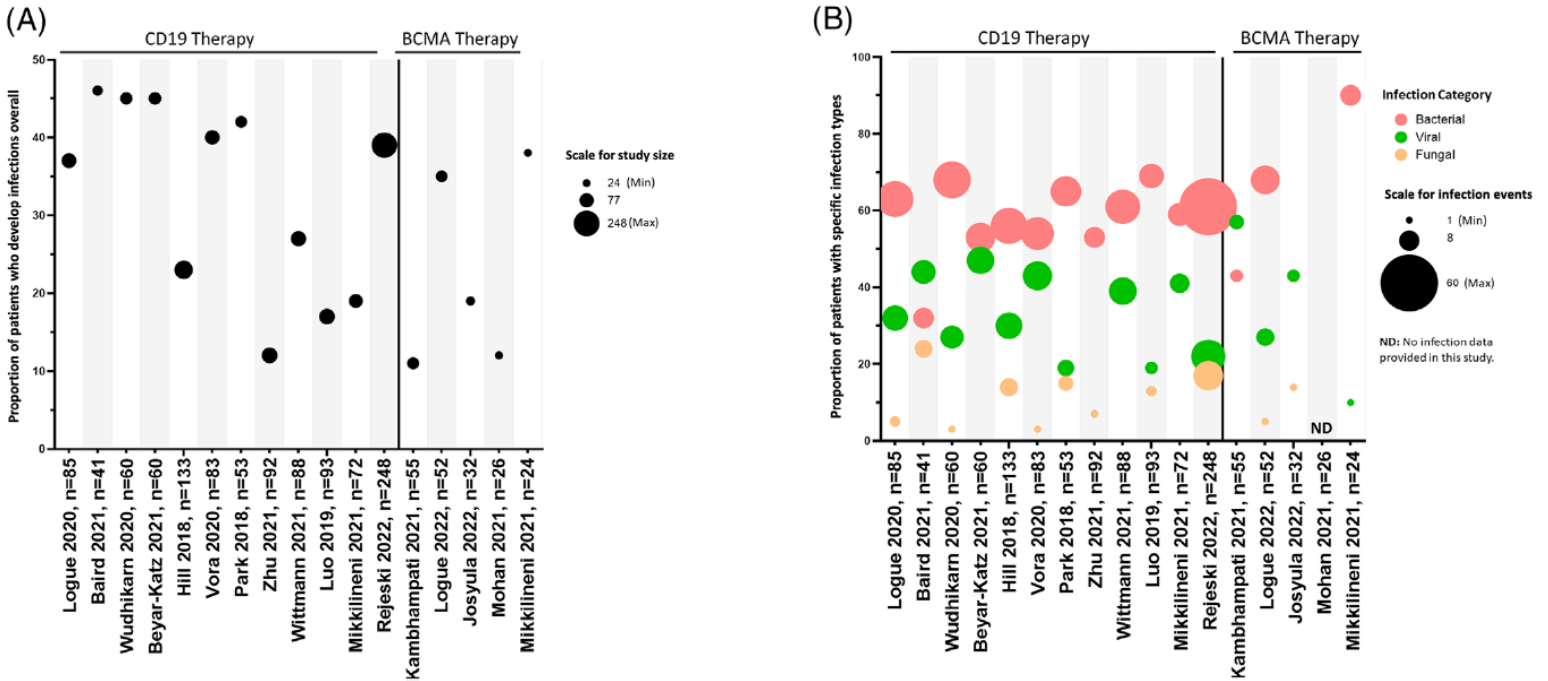
- Aplastic phenotype more frequent
- Higher incidence of pancytopenia
- Prolonged hospitalization: 54 days VS 29.5 days (p = 0.0028)
- Worse clinical outcomes: : PFS (p = 0.07), OS (p = 0.09), OR (66.6% if low risk versus 30.6% if high risk, p = 0.1)

Baseline cytopenia and elevated inflammatory markers (HEMATOTOX score) are correlated with the duration of neutropenia, and survivals but CRS and ICANS severity and peak cytokine levels are not



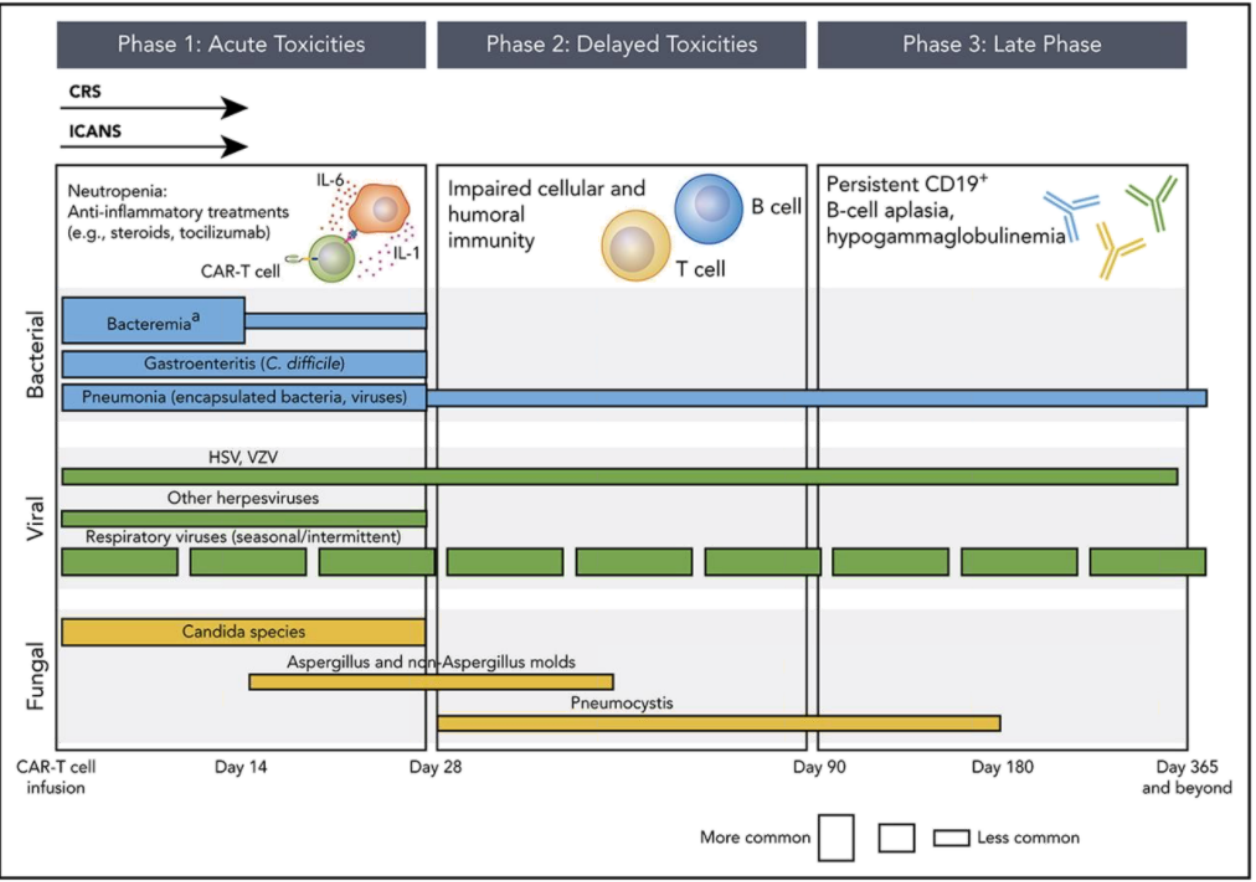
Rejeski et al. Blood 2021

Infectious risk



Eleftheria Kampouri et al. Transpl Infect Dis. 2023

Infectious Risk



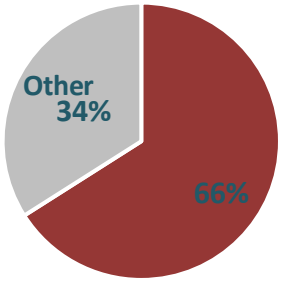
- Early (0–30 days): bacterial (neutropenia, steroids)
- Late (>30 days): viral (RSV, influenza, COVID) & herpesvirus
- Opportunistic infections: PJP, toxoplasmosis
- Infections = major cause of non-relapse mortality

Hill and Seo, Blood 2020

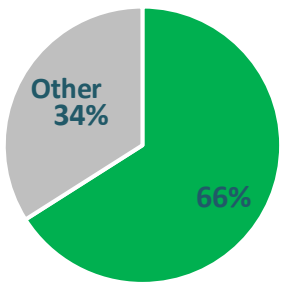
Infections are the first cause of non-relapse mortality

CAR T-cells	ZUMA-1[1]	JULIET[2]	TRANSCEND[3]	Nastoupil JCO 2020[4]	Pasquini Blood Adv 2020[5]	Jacobson Trans Cell Ther. 2022[6]	Bethge Blood 2022[7]	Kwon Haematologica 2022[8]	DESCART Lemoine 2022[9]
Study	Pivotal trial			Post-approval					
Product	Axi-Cel	Tisa-Cel	Liso-Cel	Axi-Cel	Tisa-Cel	Axi-Cel	Axi (173)/ Tisa(183)	Axi-Cel (134)/ Tisa-Cel (127)	Axi-Cel (599)/ Tisa-Cel (358)
Toxicity, non relapse mortality	3.7%	0	3%	4.4%	1.2%	3% at 3 mo	6% at 12 mo	7%/4%	4.9%

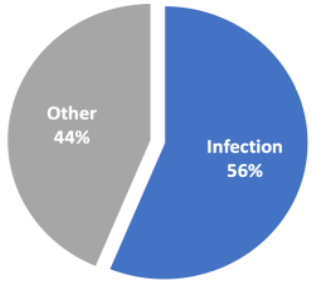
n=8/12[4]



n=10/15[10]



n=48/957[9]



Inter-trial comparisons should not be made because of differences in study design, patient populations, treatment interventions, and duration of follow-up, among others. We cannot make direct comparisons or draw conclusions from one trial to another. For descriptive purposes, toxicity results for each of the studies mentioned are listed. C. Thieblemont personal communication

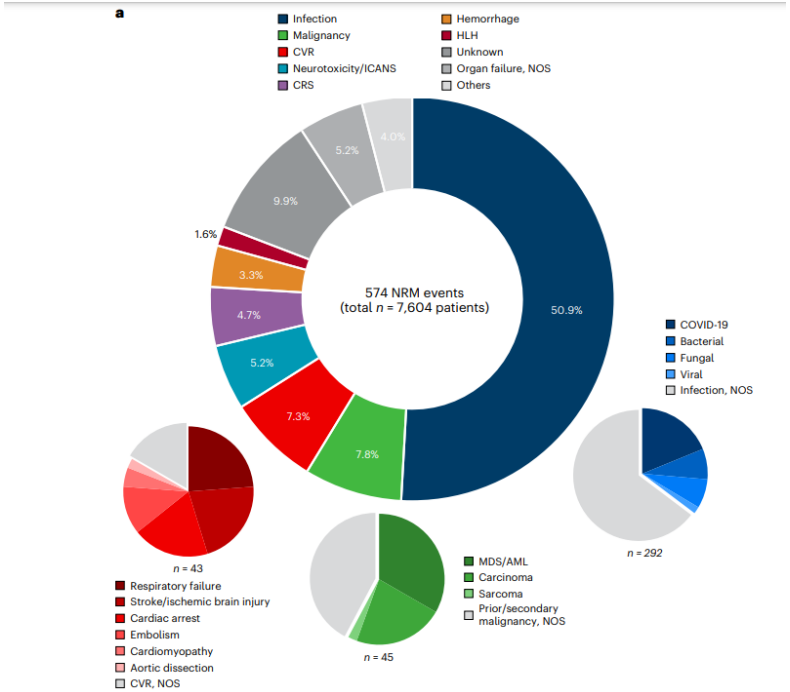
1. Locke FL, et al. Lancet Oncol. 2019; 20:31-42. 2. Schuster S, et al. NEJM. 2018;380:45-56. 3. Abramson J, et al. The Lancet.2020;396:839-852. 4. Nastoupil LJ, et al. J Clin Oncol.2020;38:3119-3128. 5. Pasquini MC, et al. Blood Adv. 2020; 4: 5414–5424.6. Jacobson CA, et al. Transplant Cell Ther.2022;28:581.e1-581. 7. Bethge WA, et al. Blood . 2022;140:349-3588. Kwon M, et al. Haematologica.2023;108:110-1213. 9. Lemoine J, et al. Blood (2022) 140 (Suppl 1): 1859–1861. 10. Rejeski K, et al. J Immunother Cancer. 2022;10:e004475

NRM is higher in MCL pts treated by brexu-cel

Cilta-cel higer NRM =15,2% followed by Brexu cel =10,6%

NRM: 53,4% infections, 7,8% other malignancy, 7% cardiovascular events

Infections and toxicity higher in RWE



nature medicine

Analysis

https://doi.org/10.1038/s41591-024-03084-6

A systematic review and meta-analysis of nonrelapse mortality after CAR T cell therapy

Received: 28 January 2024

Accepted: 22 May 2024

Published online: 8 July 2024

Check for updates

David M. Cordas dos Santos[1,2,3,4,11], Tobias Tix[4,11], Roni Shouval[5,6], Anat Gafter-Gvili[7,8], Jean-Baptiste Alberge[1,2,3], Edward R. Scheffer Cliff[1,2,9], Sebastian Theurich[4,10], Michael von Bergwelt-Baildon[4,10], Irene M. Ghobrial[1,2,3], Marion Subklewe[4,10], Miguel-Angel Perales[5,6] & Kai Rejeski[4,5,6,10]

Cordas Dos Santos DM et al. Nat Med. 2024

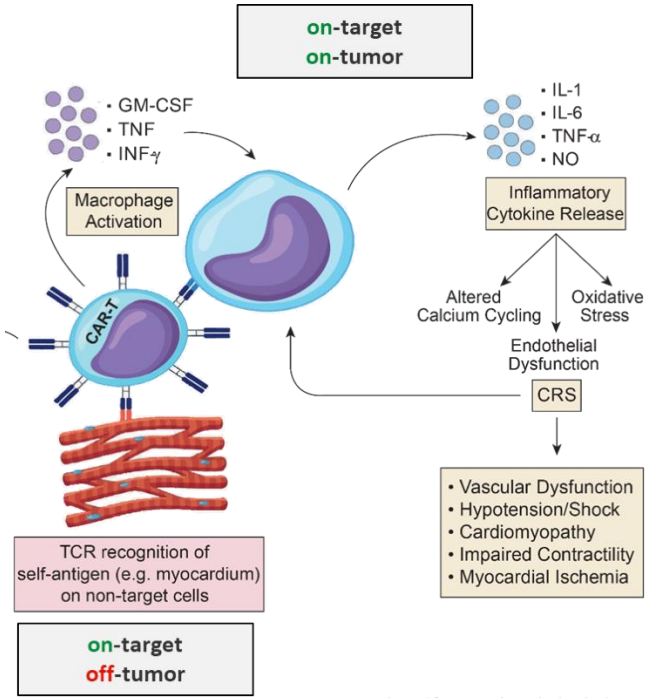
Infection Prevention:
Prophylaxis and supplementation guidelines

JACIE/EBMT

	Trials	EBMT recommendation	Comment
Neutropenia	G-CSF should be used according to published guidelines	G-CSF to shorten duration of neutropenia from 14 days post-infusion can be considered	Avoid if patient has CRS or ICANS There are theoretical concerns regarding macrophage activation
Antibacterial prophylaxis	Not recommended	Not recommended*	Can be considered in case of prolonged neutropenia and should be based on local guidelines e.g. with levofloxacin or ciprofloxacin
Anti-viral prophylaxis	Subjects should receive prophylaxis for infection with herpes virus, according to NCCN guidelines or standard institutional practice	Valaciclovir 500 mg bid or aciclovir 800 mg bd	Start from LD conditioning until 1 year post-CAR T-cell infusion and/or until $CD4^+$ count $>0.2x10^9/L$
Anti-pneumocystis prophylaxis	Subjects should receive prophylaxis for infection with *Pneumocystis pneumonia*, according to NCCN guidelines or standard institutional practice	Co-trimoxazole 480 mg once daily or 960 mg three times each week To start from LD conditioning until 1 year post-CAR T-cell infusion and/or until $CD4^+$ count $>0.2x10^9/L$	Can be started later depending on center guidelines. In case of co-trimoxazole allergy, pentamidine inhalation (300 mg once every month), dapsone 100 mg daily or atovaquone 1500 mg once daily are other agents to consider
Systemic anti-fungal prophylaxis	Subjects should receive prophylaxis for fungal infections according to NCCN guidelines or standard institutional practice	Not recommended routinely; however, consider in patients with prolonged neutropenia and on corticosteroids	In patients with prior allo-HCT, prior invasive aspergillosis and those receiving corticosteroids, posaconazole prophylaxis should be considered
IV immunoglobulins	Gammaglobulin will be administered for hypogammaglobulinaemia according to institutional guidelines. At a minimum, trough IgG levels should be kept above 400 mg/dL, especially in the setting of infection	Routine in children, consider in adults who have had infections with encapsulated organisms	Clinical evidence does not support routine use in adults following allo-HCT

Yakoub-Agha et al. Haematologica. 2020 (similar to Hill al. Blood Rev. 2019 al for IVIG)

Cardiac toxicity of CAR T-cells



Adapted from Munir et al, Blood Adv. 2024

Mechanisms:

- On-target/off-tumor and off-target effects beyond CRS (Cytokine Release Syndrome).
- Contributing factors: lymphodepletion (cyclophosphamide), systemic inflammation, and immune activation.

Incidence:

- Pivotal trials often excluded cardiac patients → underreporting of cardiovascular events (CVEs).

Clinical impact:

- Increased cardiopulmonary adverse events (tachyarrhythmias, VTEs, HF) in real-world data (FAERS)

Courtesy of Roni Shouval

Cardiovascular Complications of CAR-T: Myocardial Injury, Arrhythmias, and Shock

Myocardial Infarction/ACS

- MI reported in **1–7%**
- Primarily **Type II MI** (supply-demand mismatch)
- **Troponin** (*event triggered*) elevation observed in up to 54% of patients overall and 71% in high-grade CRS[1]

Arrhythmias

- **Incidence**: 5–12%, most commonly atrial origin
- **MSK cohort (n=236)**[2] – NHL
  - 10% develop atrial arrhythmias (primarily AF)
  - **Biomarkers**: BNP↑ (43%), Troponin↑ (17%), Ischemic ECG changes (13%)
  - **Management**: 83% needed treatment, but none were life-threatening.
  - **Outcome**: 91% converted to NSR, 17% had LV function decline on follow-up echo.

Other complications

- **Vasopressor-requiring hypotension** occurs in up to 25% of CAR-T patients
- Shock occurs in 40–50% of MACE cases, but true **cardiogenic shock** is rare
- **Cardiac arrest & CV death** are rare (typically <2%)
- **Pericardial disease** reported in a FAERS pharmacovigilance study[3]

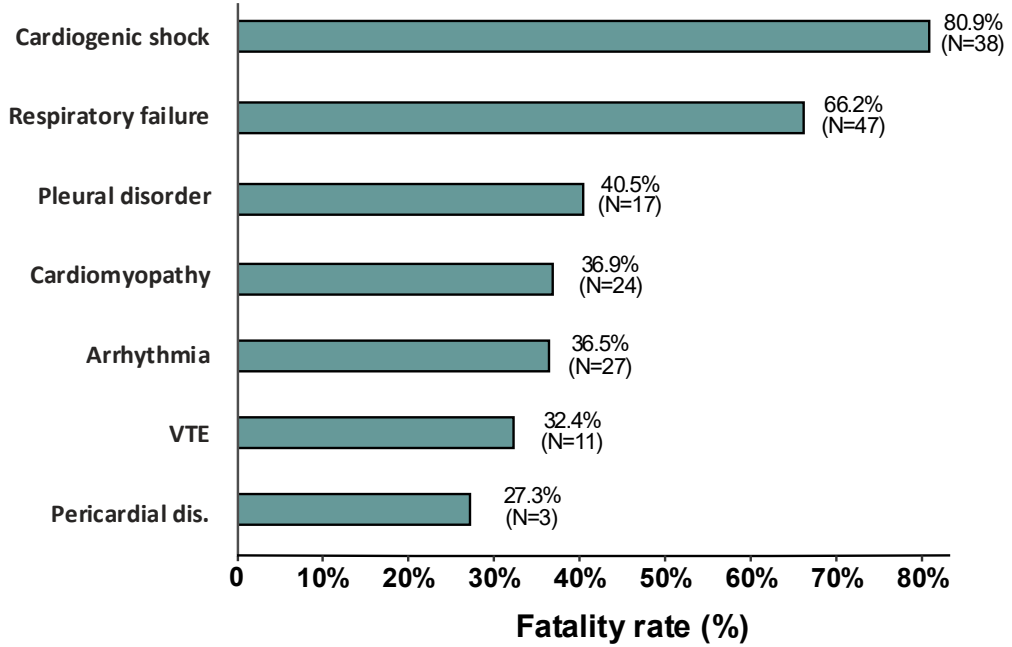
1. Alvi et al, JACC 2019; 2. Shouval et al, BJH 2024; 3. Goldman et al, JACC 2021

MACE - major adverse cardiovascular events

Courtesy of Roni Shouval

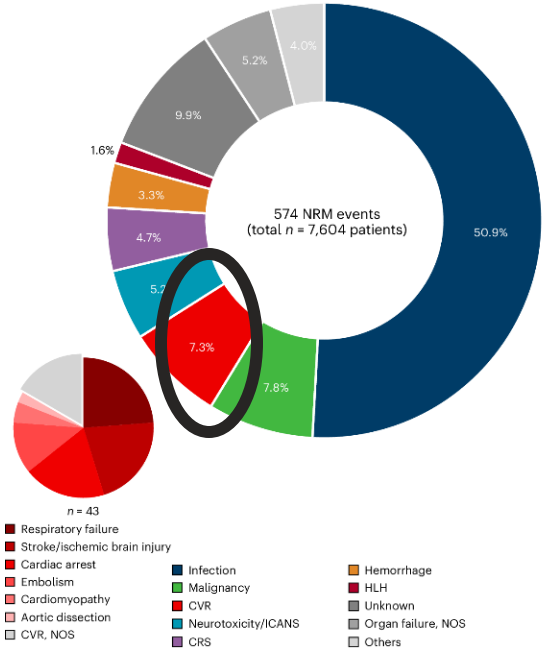
Cardiovascular AEs are a non-negligible cause of NRM

Reported Fatality Rate for CV AEs in FAERS



Goldman et al, JACC 2021; FAERS – FDA AE Reporting System;

Meta-analysis of CAR-T NRM Causes



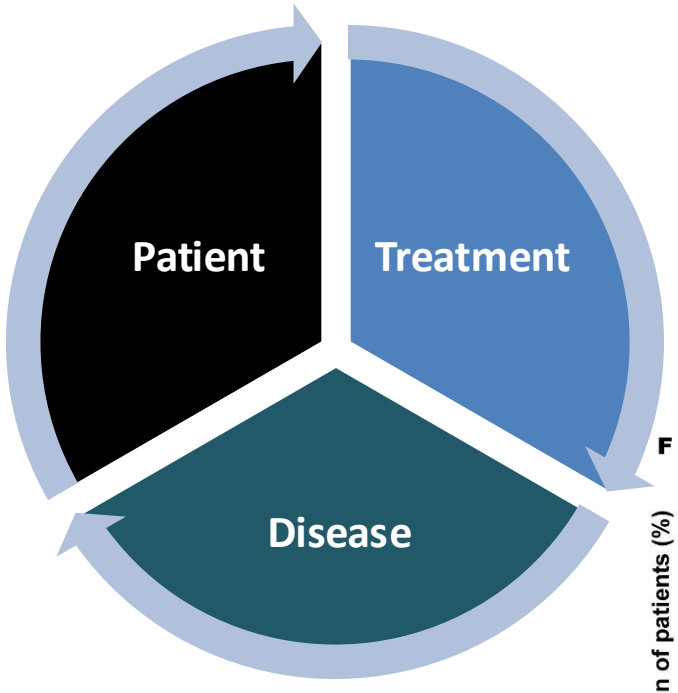
Dos Santos et al, Nature Medicine 2024

Courtesy of Roni Shouval

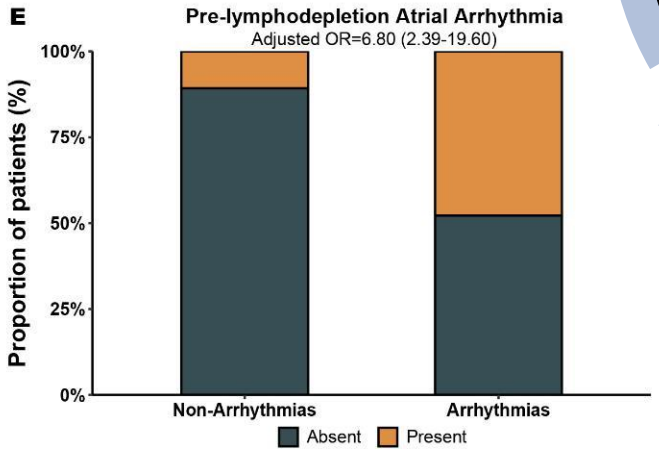
Risk Factors for Cardiotoxicity following CAR-T

Pre-existing CV Disease
- CAD
- HF/CMP
- Arrhythmia
- CV risk factors

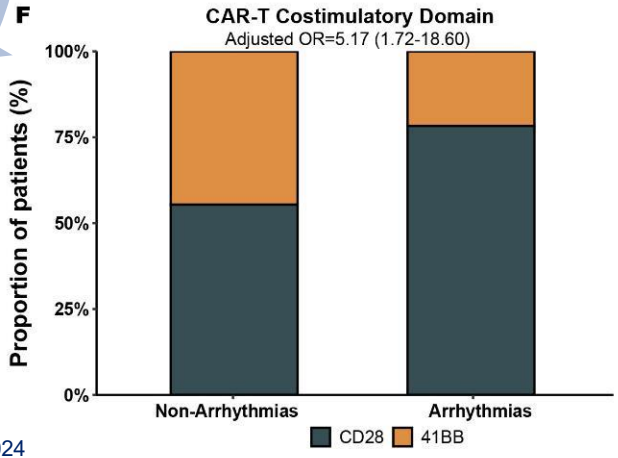
▲ Cardiac biomarkers
CKD
Older age
Low performance status



Hx of anthracycline
Hx of RT exposure
Bridging
Lymphodepletion
CAR-T product
CRS
CAR-T expansion



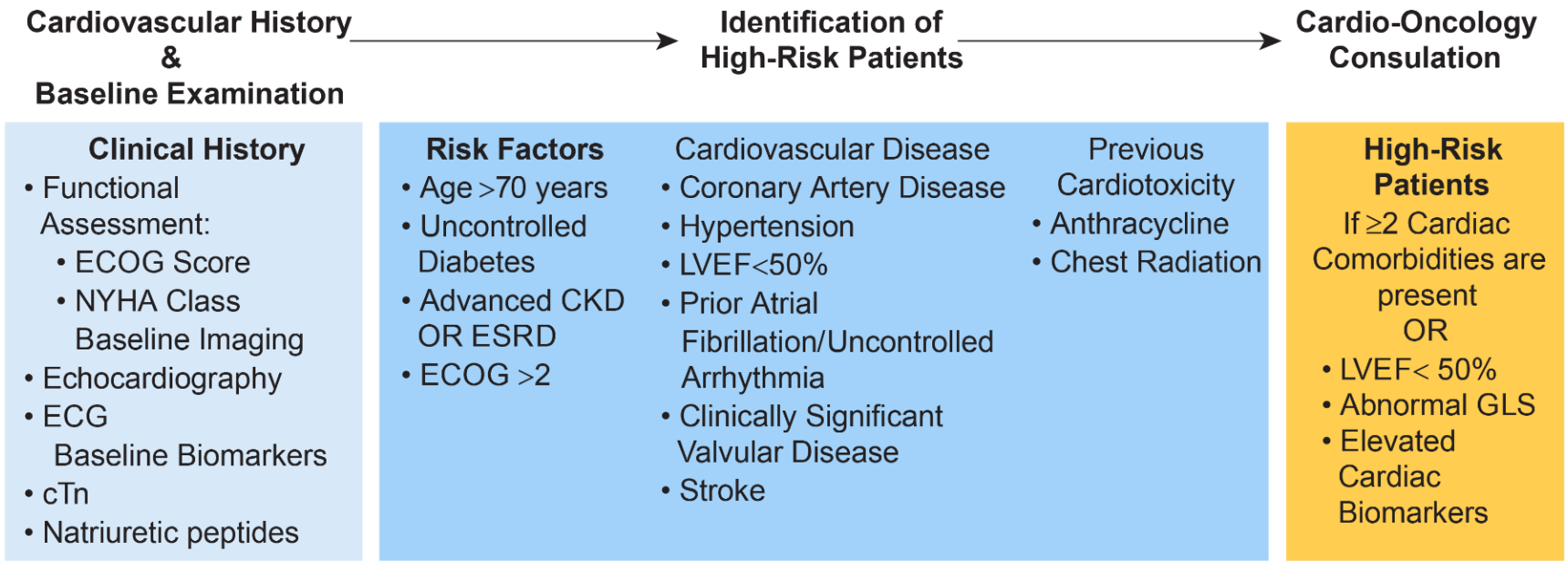
Tumor burden
Systemic inflammation



Shouval et al, BJH 2024
Palaskas et al, BMJ 2024
Munir et al, Blood Adv, 2024

Pretreatment Evaluation

Patient Considerations prior to initiating cellular therapy



GLS – Global Longitudinal Strain (LV Function)

*Personal opinion; society guidelines are available: ESC 2022 Cardio-Oncology Guidelines, NCCN Management of Immunotherapy-Related Toxicities,

Adapted from Munir et al., Blood Adv. 2024; Palaskas et al., BMJ 2024; Lyon et al., Eur Heart J 2022.

Courtesy of Roni Shouval

Management of High-risk Patients

High-Risk Patients

If ≥2 Cardiac Comorbidities are present

OR

- LVEF< 50%
- Abnormal GLS
- Elevated Cardiac Biomarkers

Pts. developing CRS2+?

Implications

Pre-infusion

- Cardiology consult
- Additional cardiac imaging/stress testing
- Optimization of CV risk factors
- Optimize heart failure/arrhythmia control

During infusion

- Close monitoring and telemetry
- Serial biomarkers in symptomatic pts.
- Aggressive management of CRS
- Low threshold for cardiac imaging and ECG

Post infusion

- Consider echocardiography 7-14 days after infusion and at 30 days
- Cardiac follow-up ~1 month after CAR-T
- Low threshold to reintroduce cardioprotective medications including antiaggregants and anticoagulants

Courtesy of Roni Shouval

Secondary Malignancies (SPM) after CAR T-Cell Therapy

Long-term risks include second primary malignancies (SPMs) and therapy-related myeloid neoplasms (t-MN).

Incidence & Types:
- Overall SPM incidence ~5–15% across studies.
- Hematologic (MDS/AML/t-MN) and non-melanoma skin cancers predominate.
- Median latency to t-MN ~14–16 months; can occur as early as 3–6 months.

Risk Factors:
- Older age, higher MCV, high-grade ICANS, and pre-existing clonal hematopoiesis (e.g., TP53 mutations).
- CHIP in ~85% of t-MN cases → suggests clonal selection under cytotoxic stress.

Mechanisms & Cases:
- Rare CAR-transgene positive malignancies (e.g., T-cell lymphoma) reported.
- Regulatory agencies (FDA, EMA) recommend lifelong monitoring.

Clinical Implications:
- Genomic screening for CHIP prior to CAR T-cell therapy may stratify risk.
- Long-term hematologic and oncologic surveillance is warranted.

Tix et al., Clin Cancer Res 2024 | Nature 2025 | Umyarova et al., J Hematol Oncol 2025

SPM - a Metanalysis

5,517 patients receiving CAR T for B-cell malignancies (LNH and MM)

SPMs categorized as hematologic, solid, non-melanoma skin, or indeterminate.

Incidence & Distribution

Overall incidence: ≈ 5.8 % (median follow-up ≈ 21.7 months).

Distribution (pooled data):

- Hematologic ≈ 37 % (mainly MDS/AML)
- Solid tumors ≈ 27 %
- Non-melanoma skin ≈ > 25 %

Longer f-up, higer incidence (p=0,04)

Skin cancers: mostly SCC and BCC (rare melanoma cases).

Solid tumors: lung (NSCLC/SCLC), prostate, breast, bladder, thyroid, others=> incidence comparable to the rest of the population.

Risk Factors (univariate analyses)

Age = strongest risk factor (HR ~ 1.05 per year).
Patients < 65 y had significantly lower risk of SPMs.

NRM due to second malignancies = 7,8%

No difference in CAR T product but higer incidence in higer dose LD regimens (not significant).

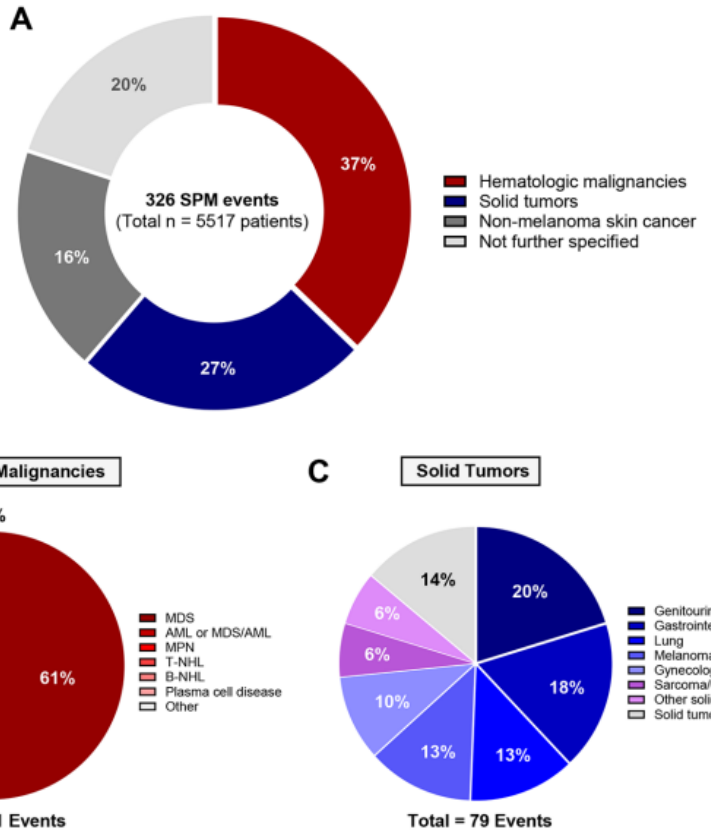
No difference of SPM in CAR T-cells arm vs SOC arm in randomized studies.

Tix et al., Clin Cancer Res 2024

SPM - a Metanalysis

SPM development appears **multifactorial**:

- Prior chemo/radiotherapy and cumulative genotoxic stress.
- Pre-existing **clonal hematopoiesis (CHIP)** (e.g., TP53 mutations) may predispose.
- No firm evidence that CAR transgene insertion causes SPMs, though vigilance is needed.



T-cell malignancies:

Only 5 cases of T-cell malignancy were described, accounting for just 4.1% of all hematological SPMs and 1.5% of all SPMs.

= 0.09% (95% CI 0.04%–0.2%)= 5 cases: 3 were tested for the presence of CAR transgene, with only 1 being classified as positive in a preliminary report.

Tix et al., Clin Cancer Res 2024

Quality of Life Issues - Work & Reintegration

- Physical: fatigue, pain, cognitive impairment
- Psychological: anxiety, depression, sleep disorders
- Social: family/sexual health, caregiver stress
- Fertility: preservation should be discussed

- Higher unemployment, disability after CAR-T
- Return to work is often slow & limited
- Support: adapted schedules, pre-return visits, social aid

New healthcare figures

Collaboration: hematologists, ID specialists, psychologists, fertility experts, Social workers, GPs, community networks

+ new figures => **APN= Advanced Practice Nurse**

A state-certified nurse with **at least 3 years of professional experience** who has completed a **master's level university program**.

- Different Specialization options: Oncology and Hemato-oncology/Psychiatry and Mental Health/Emergency Care/Stable Chronic Diseases/ Chronic Kidney Disease, Dialysis, and Kidney Transplantation.

Missions:

- **Ethical Decision-Making** – applying professional ethics to complex clinical situations.
- **Collaboration** – working effectively within multidisciplinary teams.
- **Leadership** – promoting innovation and quality in healthcare practices.
- **Expertise and Coaching** – providing clinical expertise, guidance, and mentorship.
- **Consultation** – offering specialized advice for patient management and care pathways.
- **Research and Evidence-Based Practice** – integrating research findings into clinical practice to improve patient outcomes.

Conclusions

- **Long-term follow-up is essential** after CAR-T therapy to monitor relapse, late toxicities, infections, and secondary malignancies.
- **Cardiac and infectious surveillance** should be systematically integrated into CAR-T pathways.
- **Non-relapse mortality** is increasingly linked to infections and cardiovascular events — highlighting the need for proactive prevention and multidisciplinary care.
- **Predictive tools** (e.g., CAR-HEMATOTOX, E:T ratio) can help identify patients at risk of poor outcomes or prolonged cytopenias.
- **Psychosocial and quality-of-life issues** require structured support, including reintegration and fertility counseling.
- **New professional roles** (e.g., Advanced Practice Nurses) are key to ensuring continuity, coordination, and patient-centered care.
- **Future directions:** harmonize long-term follow-up protocols, refine risk stratification, and integrate real-world data to optimize survivorship.

Thanks!

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CAR T cells

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