CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, UNAHOTELS Galles

23 maggio 2025

Nuovi farmaci in ematologia e rischio infettivo

Chiara Cattaneo

Ematologia – ASST Spedali Civili - Brescia

Disclosures of Chiara Cattaneo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Jazz							Travel Grant
Johnson&Johnson							Travel Grant
Mundipharma						x	

"Although targeted therapeutic agents demonstrate a narrow spectrum of toxicity, primarily due to their specific signaling pathways, they have the potential to cause downstream path inhibition, which can alter the immune system"

Andreescu Life 2023

"Infections are the most common complication of treatment with novel immunotherapies"

Ludwig Blood Adv 2024

Targeted therapies and immune sequelae

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG [1]	Neutropenia
CD20	Rituximab Ofatumumab Obinutuzumab	+++	-	+	++ [2]
CD52	Alemtuzumab	++	+++	+	+ [3]
CD38	Daratumumab	+	+	-	+
SLAMF7	Elotuzumab	-	-	-	-
CD19/CD3	Blinatumomab	+++	+	++	++
BTK	Ibrutinib Acalabrutinib Zanubrutinib	++	-	+	+
PI3K	Idelalisib Copanlisib Duvelisib	++	+	-	+
JAK	Ruxolitinib	-	+	-	-
BCL-2	Venetoclax	-	-	-	++

Little J Fungi 2021

Target therapy and infections

In lymphoproliferative syndromes

- Signaling pathway inhibitors
  - *BTK-i*
  - *Venetoclax*

- Immunotherapy
  - *Bispecific MoAb*
  - *CAR-T*

Target therapy and infections

In lymphoproliferative syndromes

- **Signaling pathway inhibitors**
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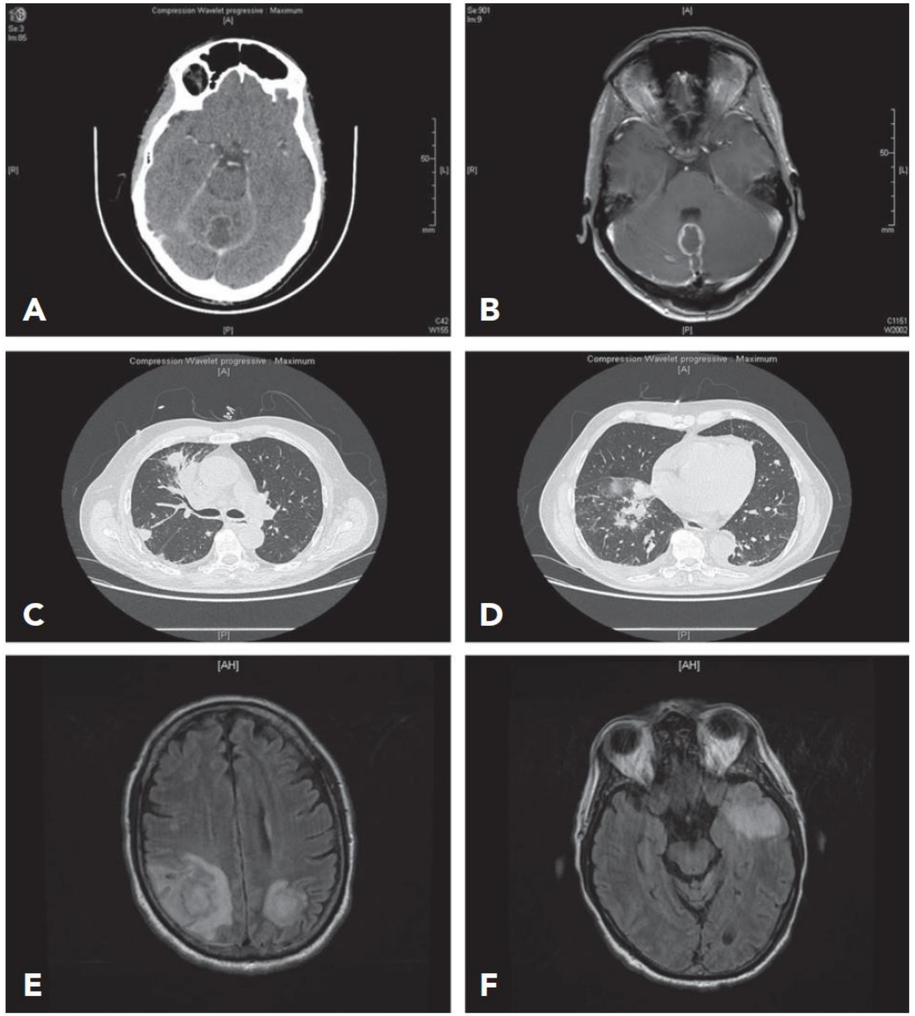
- Immunotherapy
  - *Bispecific MoAb*
  - *CAR-T*

Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib

blood® 26 APRIL 2018 | VOLUME 131, NUMBER 17

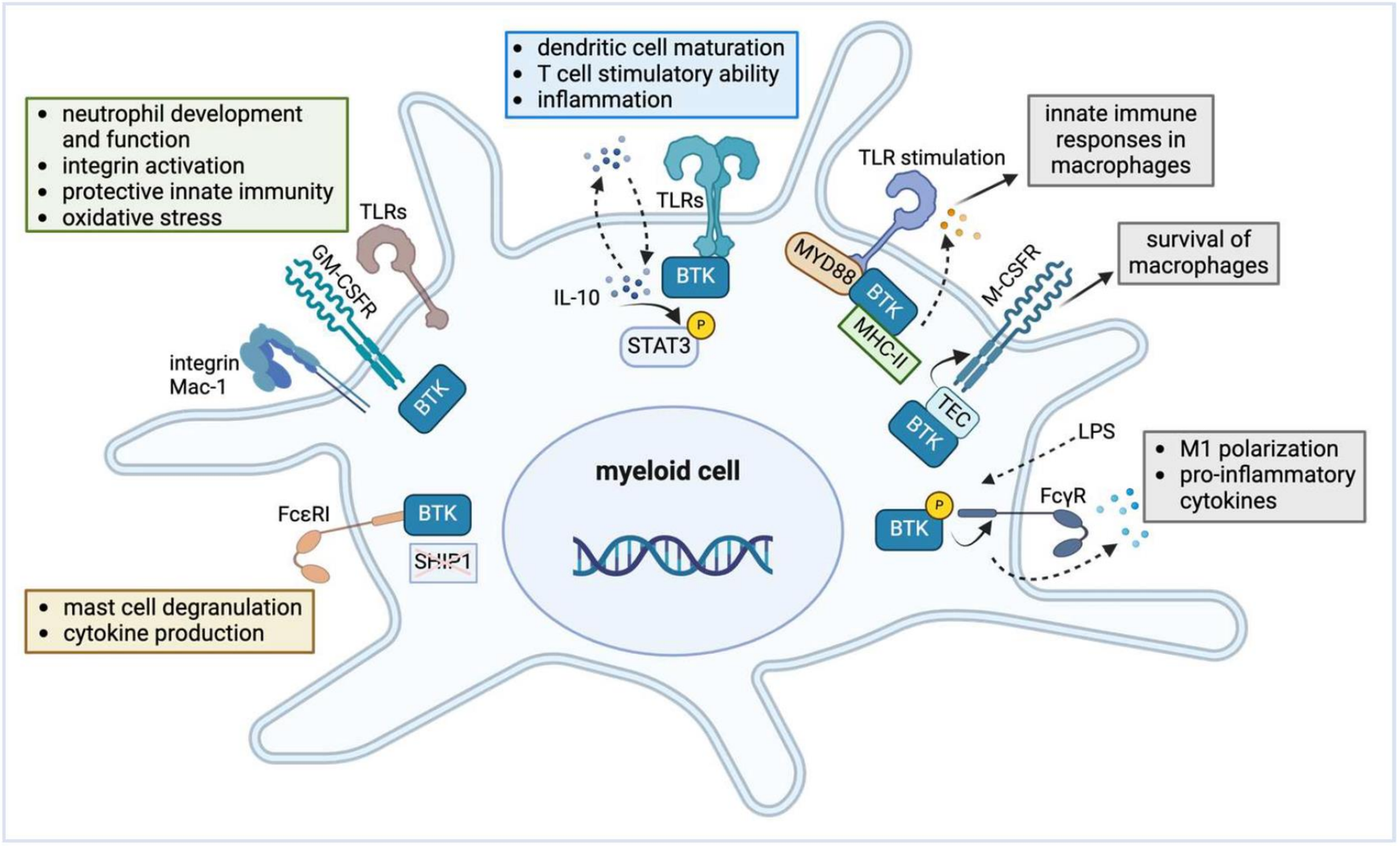
David Ghez,[1] Anne Calleja,[2] Caroline Protin,[3] Marine Baron,[4] Marie-Pierre Ledoux,[5] Gandhi Damaj,[6] Mathieu Dupont,[7] Brigitte Dreyfus,[8] Emmanuelle Ferrant,[9] Charles Herbaux,[10] Kamel Laribi,[11] Ronan Le Calloch,[12] Marion Malphettes,[13] Franciane Paul,[14] Laetitia Souchet,[4] Malgorzata Truchan-Graczyk,[15] Karen Delavigne,[16] Caroline Dartigeas,[17] and Loïc Ysebaert,[3] on behalf on the French Innovative Leukemia Organization (FILO) CLL group

- Between **2013 and 2017**, from 16 French centers 33 cases of invasive fungal infections in patients receiving ibrutinib alone or in combination
- Invasive **aspergillosis** was **overrepresented** (27/33) and was associated with **cerebral localizations** in **40%** of the cases
- **Most infections** usually occur **during the first months of treatment**, often in patients with **other risk factors** for fungal infections



The immunomodulatory effect of BTK-i

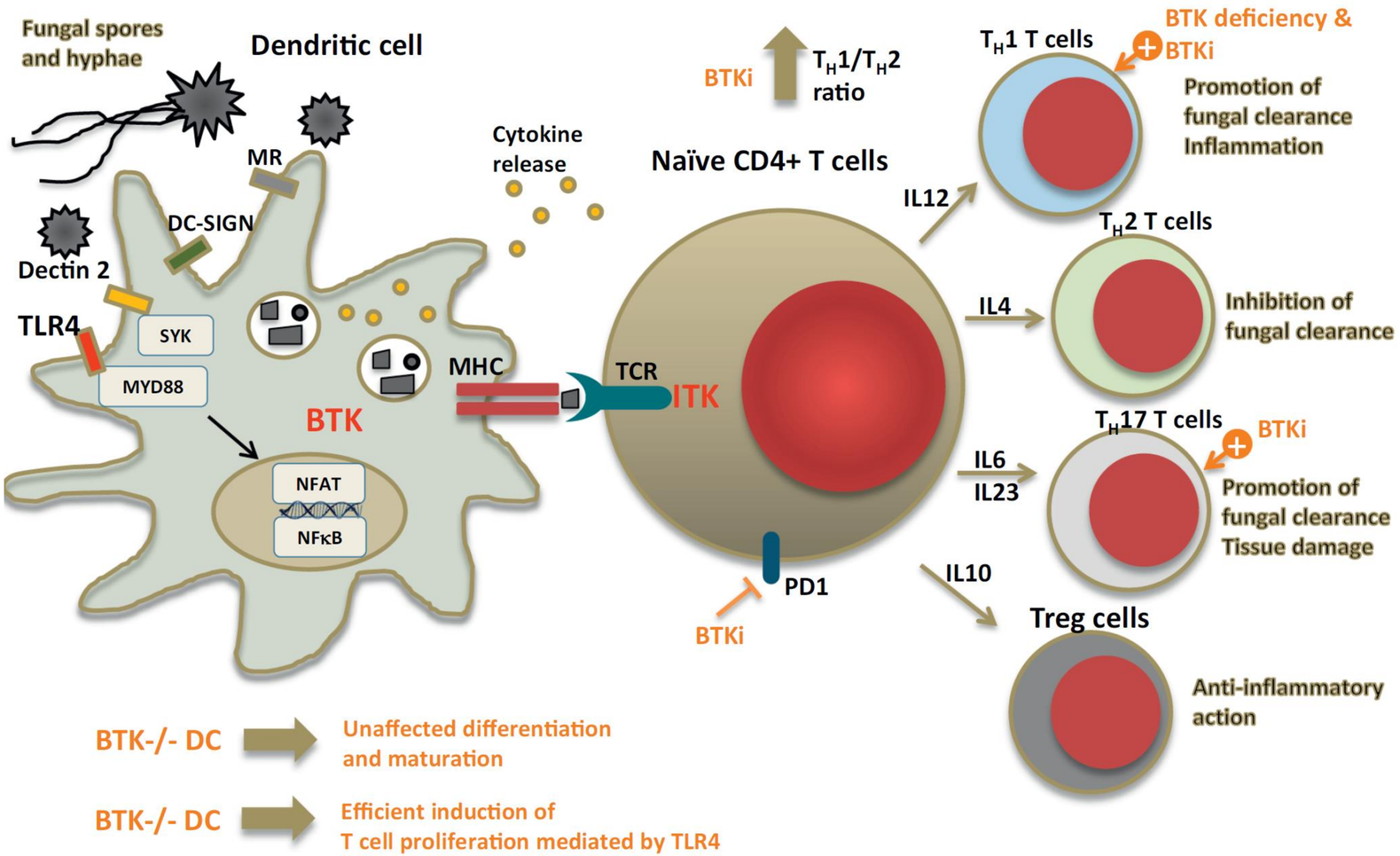
- The expression of **BTK** is **not restricted to B cells**
- BTK is critical for regulating myeloid cell-mediated innate host defense, particularly in **neutrophils** and **macrophages**



Jiang Cancers 2024

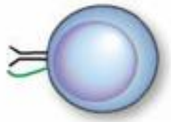
BTKi and adaptive immunity

- **Dendritic cells** deficient for BTK efficiently promotes T cell activation
- In **T lymphocytes**, **ibrutinib suppresses the survival of TH2** cells, down-regulates PD-1 expression and reduces T regulatory cells, whereas **favors TH1 and TH17 accumulation**
- T lymphocytes are spared from activation-induced cell death and efficiently secretes IFN-γ in response to inflammatory stimuli in the presence of ibrutinib



Maffei Blood rev 2020

Differences between BTKi

Adverse events	Cell type	Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
Infection	B-lymphocyte 	BTK	⊣	⊣	⊣
		TEC	⊣	n.i.	⊣
	T-lymphocyte 	ITK	⊣	n.i.	n.i.
		TEC	⊣	n.i.	⊣
		RLK/TXK	⊣	⊣	⊣
	Macrophage Neutrophil 	BTK	⊣	⊣	⊣
		TEC	⊣	n.i.	⊣

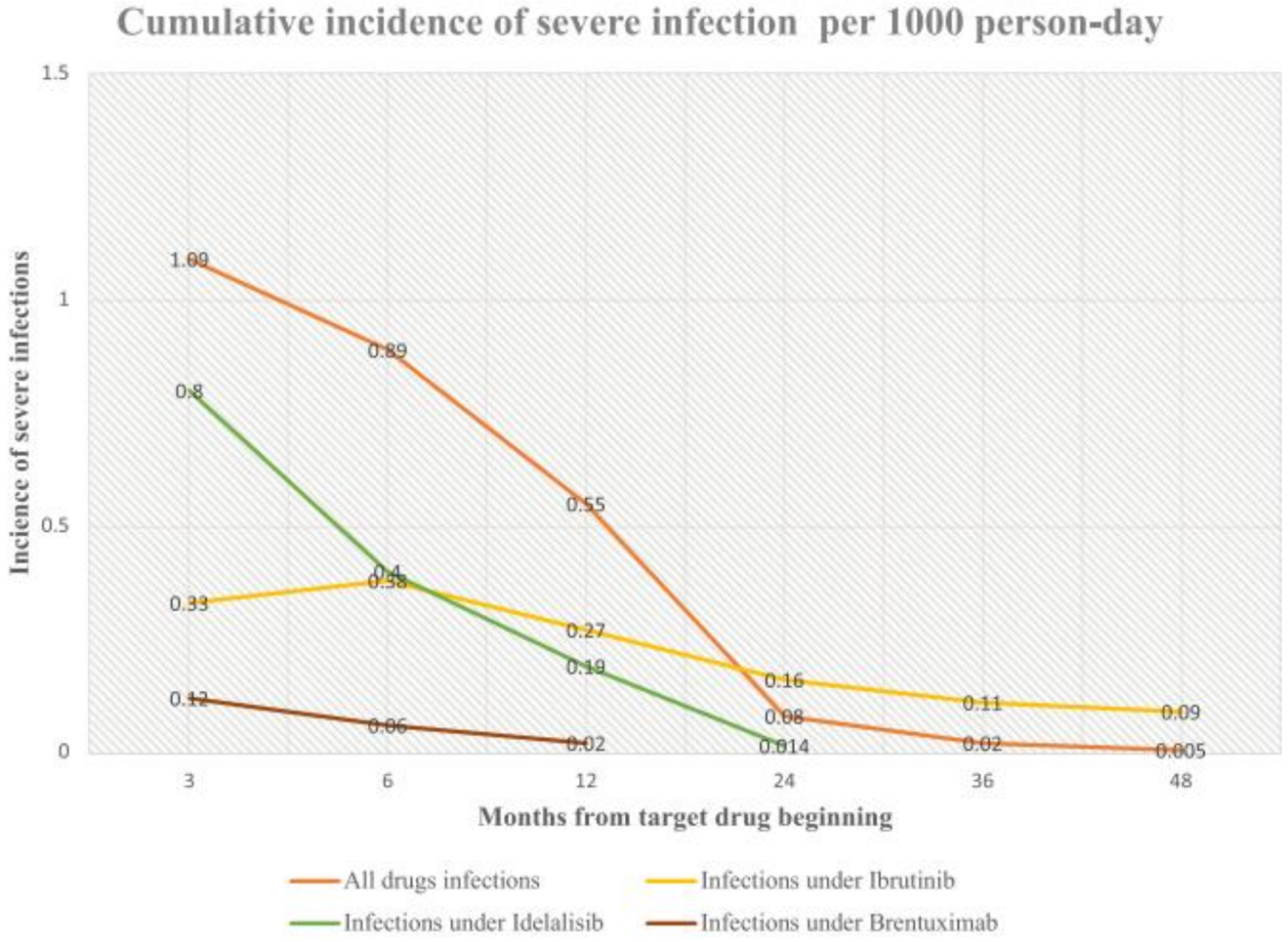
Estupiñán Front Cell Dev Biol 2021

Ibrutinib and fungal infections

Reference	Patients	All IFI, n (%)	Aspergillosis, n (%)	Candida, n (%)	Pneumocystis, n (%)	Cryptococcus, n (%)	Others
Grommes, et al. 2017[1]	20 NHL	/	1 (5)	/	/	/	
Ruchlemer, et al. 2017[2]	28 CLL	28	18 (64)	/	/	/	10
Duma, et al. 2017[3]	30 CLL	5 (4)	5 (4)		/	/	
Lionakis, et al. 2017[4]	18 CNS NHL	8	7 (39)	/	1 (5.5)	/	
Ghez, et al. 2018[5]		33	27		1	4	1
Choquet, et al. 2016[6]	18 NHL	1	2	/	/	/	
Varughese, et al. 2018[7]	213 NHL 165 CLL	6 (3) 10 (6)	8 (2.1) + 1 IA and PJP	1 (0.3)	3 (0.8)	3 (0.8)	10
Gaye, et al. 2018[8]	CLL	2	2				

1. Grommes, et al. Cancer Cell. 2017;31(6):731–733; 2. Ruchlemer R et al ASH 2017 Abstract 4323; 3. Duma N et al ASH 2017 Abstract 4327; 4. Lionakis, et al. Cancer Cell. 2017;31(6):833–843; 5. Ghez, et al. Blood. 2018;131(17):1955–1959; 6. Choquet et al ASH 2016, Abstract 784; 7. Varughese, et al. Clin Infect Dis. 2018;67(5):687–692; 8. Gaye, et al. Med Mal Infect. 2018;48(4):294–297.

Severe infections in patients with lymphoproliferative diseases treated with new targeted drugs: A multicentric real-world study



Severe infections
105/462 **(23%)**
0.55 per 1000 person-days
1 severe infection over 7.2 y

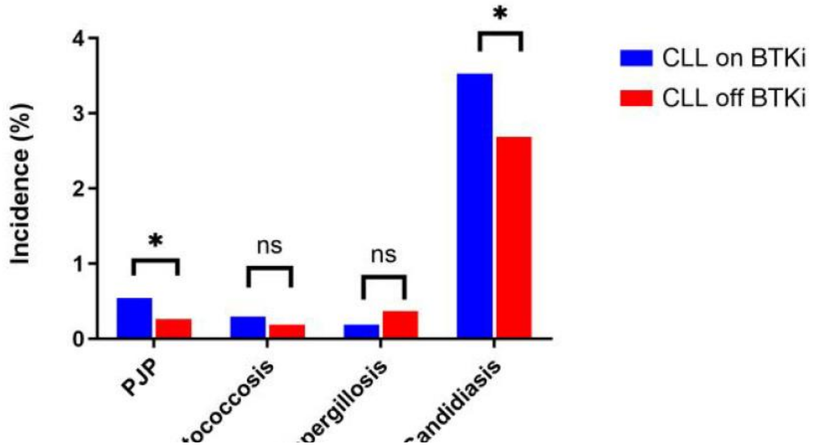
Infante et al. Cancer Med 2021

Risk of Invasive Fungal Infections in Patients With Chronic Lymphocytic Leukemia Treated With Bruton Tyrosine Kinase Inhibitors: A Case-Control Propensity Score–Matched Analysis

Nelson Iván Agudelo Higuita,[1,2] Daniel B. Chastain,[3] Brian Scott,[1] Syeda Sahra,[1] Lilian Vargas Barahona,[4] José Henao Cordero,[1] Alfred L. H. Lee,[5] Jose Tuells,[6] and Andrés F. Henao-Martínez[7]

Open Forum Infectious Diseases

MAJOR ARTICLE



- 5358 matched patients with CLL
- Anti-CD20 monoclonal antibodies were administer
- IFIs: 4.6% i
in patients
- Annual rates of 0.9% and 0.7%, respectively
- Additional 1% risk of IFI in patients with CLL while on a BTKi over 5 years compared to those not on a BTKi

No antifungal prophylaxis!

› Harm With Invasive Fungal
ytic Leukemia on a Bruton

Invasive Fungal Infection	Episodes[a], No. (%)	Relative Risk (95% CI)	NNH
Pneumocystis jirovecii pneumonia	29 (0.5%)	2.1 (1.1 - 4.0)	358
Cryptococcosis	16 (0.3%)	1.6 (0.7 - 3.5)	894
Aspergillosis	10 (0.2%)	0.5 (0.2 - 1.1)	536[b]
Invasive candidiasis	189 (3.5%)	1.3 (1.1 - 1.6)	120

Abbreviation: NNH, number needed to harm.

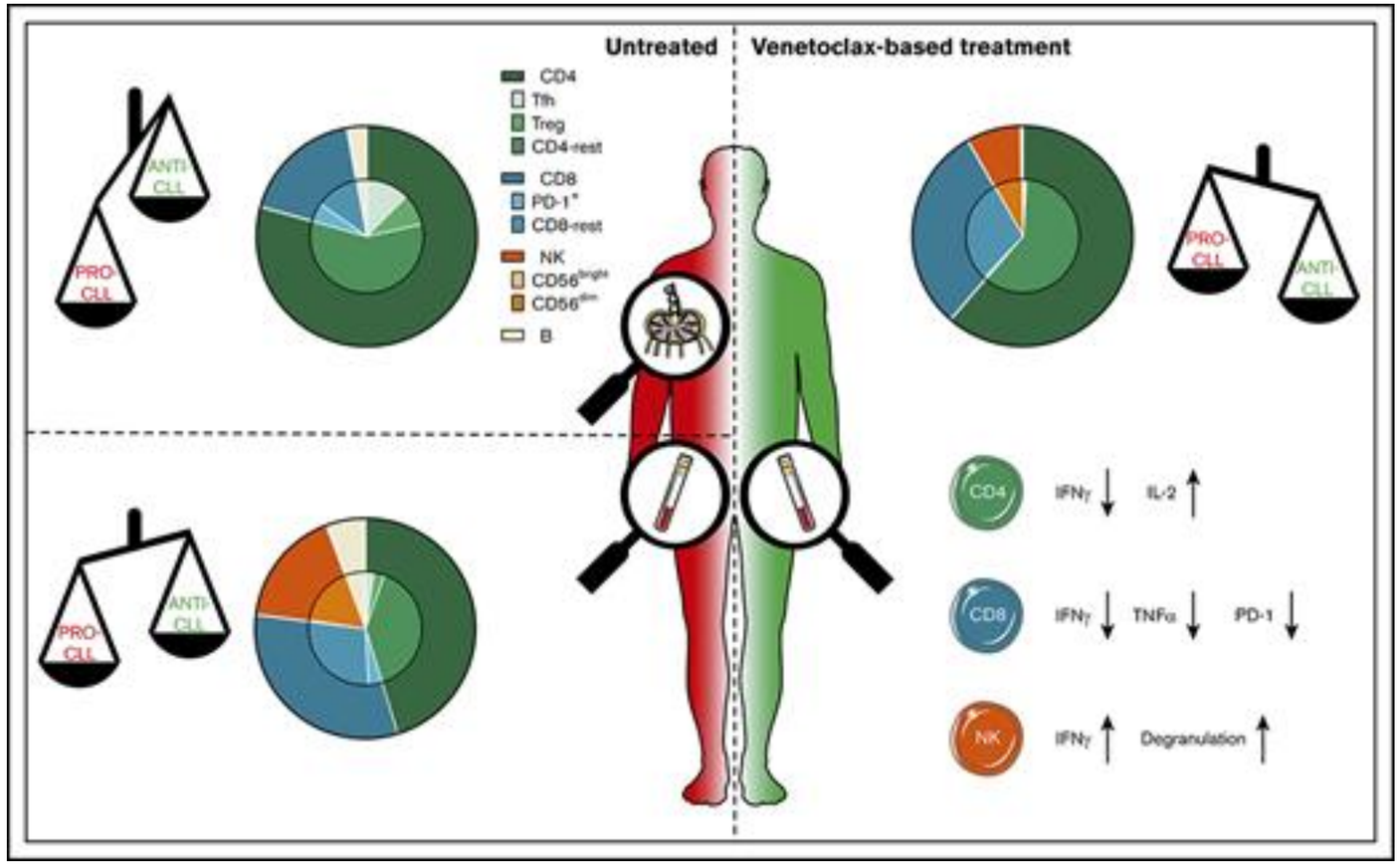
[a]Among 5358 matched patients with chronic lymphocytic leukemia on a Bruton tyrosine kinase inhibitor.

[b]Number needed to treat.

Distinct immune composition in lymph node and peripheral blood of CLL patients is reshaped during venetoclax treatment

blood advances
10 SEPTEMBER 2019 • VOLUME 3, NUMBER 17

Iris de Weerdt,[1,2,*] Tom Hofland,[1,2,*] Renate de Boer,[1,2] Johan A. Dobber,[1] Julie Dubois,[1] Denise van Nieuwenhuize,[1,2] Mehrdad Mobasher,[3] Fransien de Boer,[4] Mels Hoogendoorn,[5] Gerjo A. Velders,[6] Marjolein van der Klift,[7] Ester B. M. Remmerswaal,[2] Frederike J. Bemelman,[8] Carsten U. Niemann,[9] Sabina Kersting,[10] Mark-David Levin,[11] Eric Eldering,[2,12] Sanne H. Tonino,[1,12,†] and Arnon P. Kater[1,12,†]



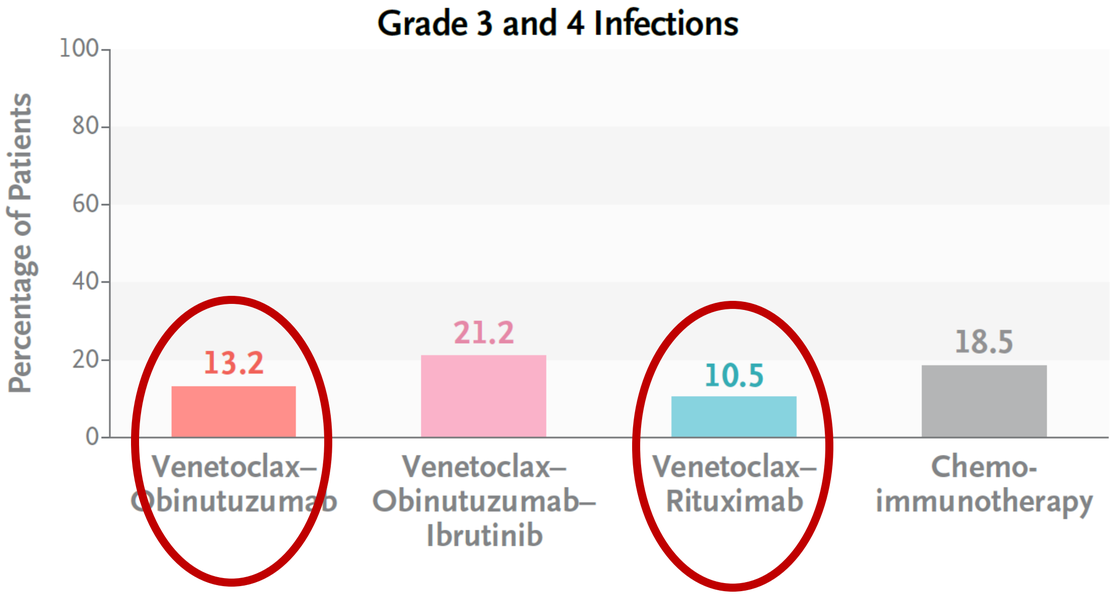
- **CLL-derived LNs** contained twice the amount of suppressive **regulatory T cells (Tregs) and CLL supportive follicular T helper (Tfh) cells** compared with PB
- **Venetoclax-based treatment** led to deep responses in the majority of patients, but also to **decreased absolute numbers of B, T, and NK cells.** Tfh cell, Treg, and PD-11 CD81 T cell numbers were reduced more than fivefold after venetoclax-based therapy, and **overproduction of inflammatory cytokines** was **reduced**. Furthermore, we observed **restoration of NK cell function**
- Venetoclax-based regimens reduced the immunosuppressive footprint of CLL, suggesting **immune recovery after the elimination of leukemic cells**

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia

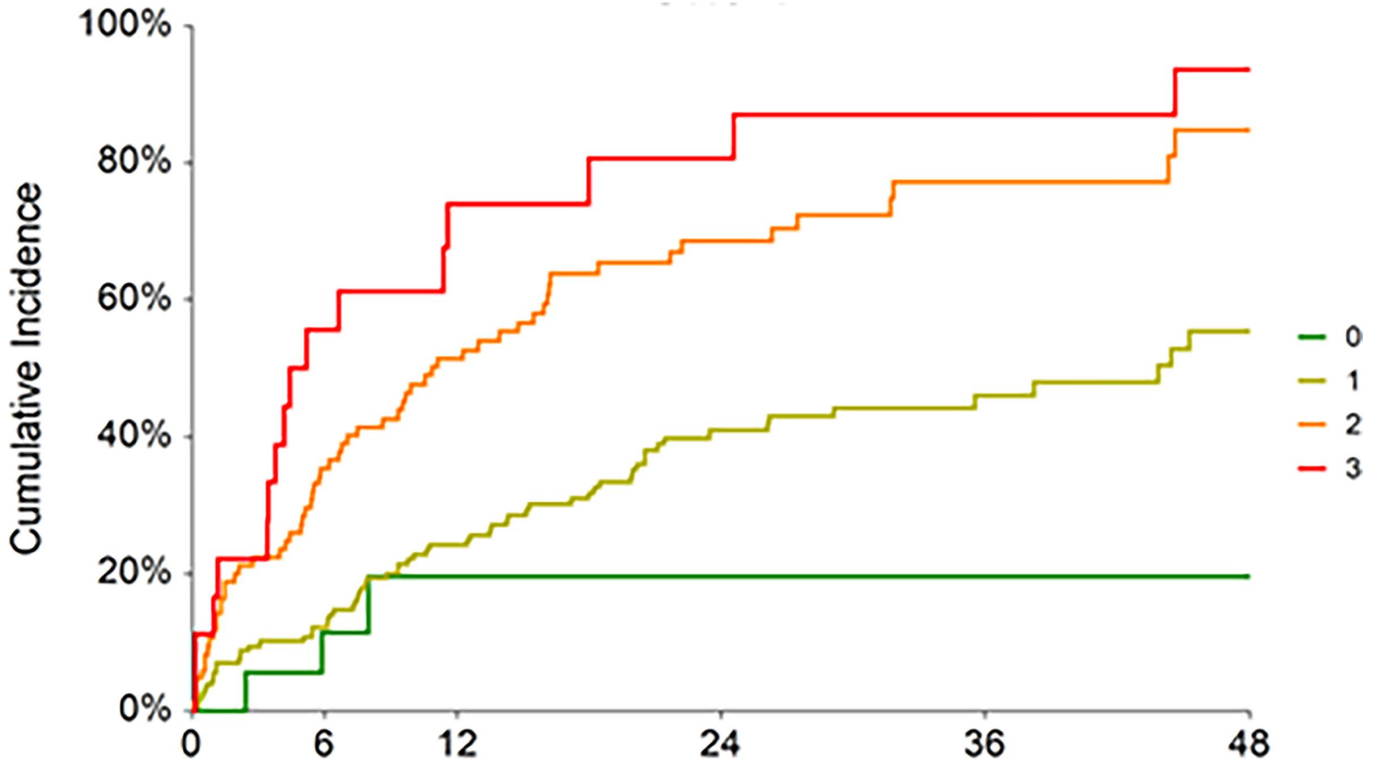
Eichhorst B et al. DOI: 10.1056/NEJMoa2213093



- **Severe infections** were more frequent in the **triple therapy** and **chemoimmunotherapy** groups than in the other two groups

Venetoclax infectious risk score to identify patients with chronic lymphocytic leukemia at high infectious risk during venetoclax treatment: A multicenter SEIFEM study

Am J Hematol. 2024;99:982–984.



- 287 CLL patients treated with venetoclax single agent or venetoclax plus anti-CD20 antibody (R or O)
- 285 infections of any grade, in 158 patients (55%)
- Median time to first infection was 219 days for any grade infection and224 days for grade 3–5 infections

Risk factor	HR (95% CI)
COPD	2.04 (1.37-3.03)
Previous infections	1.99 (1.43-2.76)
≥ 1 previous treatment	2.59 (1.14-5.89)

Autore Am J Hematol 2024

Mind the DDI…!

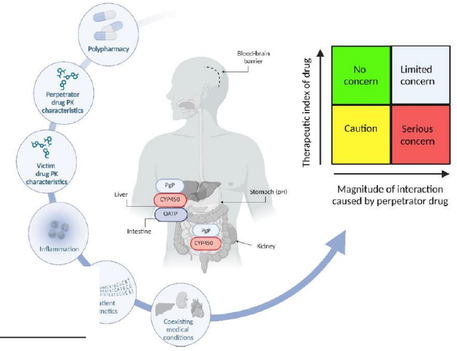


Table 8. Triazole drug interactions with targeted therapies used for AML, ALL and transplantation

Therapy	Approved dose	Strong CYP3A4 inhibitor[a]	Moderate CYP3A4 inhibitor[b]	Strong CYP3A4 inducer[c]
Venetoclax	400–600 mg q24h	Dose adjustment (75% reduction venetoclax)	Dose adjustment (50% reduction venetoclax)	Avoid
Ruxolitinib	10 mg q12h	For patients undergoing treatment of GVHD, monitor closely, consider dose reduction to 5 mg q12h	Monitor carefully and consider dose reduction	Monitor therapy and increase dose if needed
Ibrutinib	420 mg q24h (CLL/WM/ cGVHD) 560 mg q24h (MCL)	Reduce dose of ibrutinib to 70 mg q24h or 140 mg every other day	Reduce dose to 140 mg q24h	Avoid
Acalabrutinib	100 mg q12h	Avoid; for short-term therapy it is recommended to stop acalabrutinib for 7 days	No dose adjustment; monitor patients carefully for adverse reactions	Avoid
Zanubrutinib	160 mg q12h	Reduce zanubrutinib dose by 75% to 80 mg q24h	Reduce dose by 50% to 80 mg q12h	Avoid

Lewis R J Antimicrob Chemotjer 2024

Don’t forget the *old* drugs for DDI…

Table 5. Key triazole antifungal/respiratory drug interactions

Interacting drug	Potential severity of interaction					Antifungal modification	Interacting drug modification
	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole		
Prednisolone/ prednisone	+	+	++	+	–	None	Reduce prednisolone/ prednisone dose by 30% with voriconazole
Methylprednisolone	++	++	++	++	++	None	Reduce methylprednisolone dose by 50%–60%
Dexamethasone	++	++	++	++	++	None	Reduce dexamethasone dose by 50%–60%, or observe for adverse corticosteroid adverse effects

Concomitant triazole therapy also increased the exposure to both methylprednisolone and dexamethasone, resulting in the suppression of endogenous cortisol secretion

Lewis R J Antimicrob Chemotjer 2024

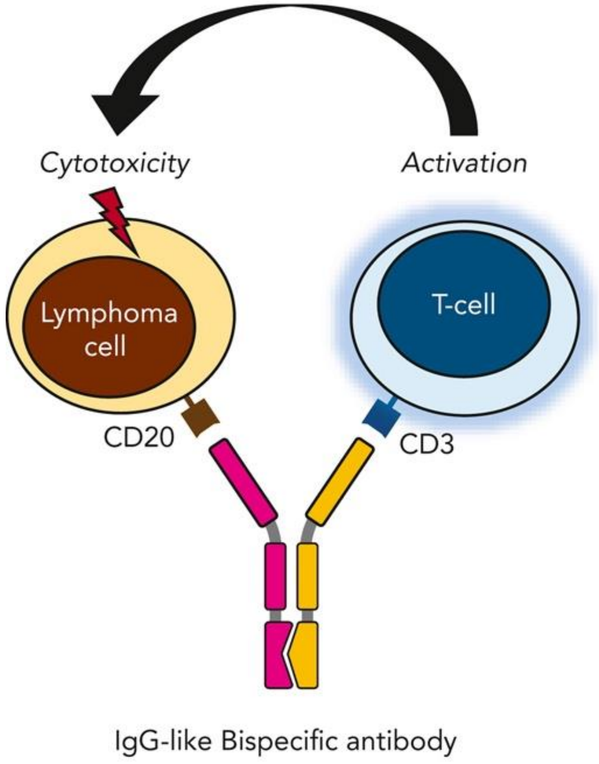
Target therapy and infections

In lymphoproliferative syndromes

- Signaling pathway inhibitors
  - *BTK-i*
  - *Venetoclax*

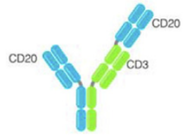
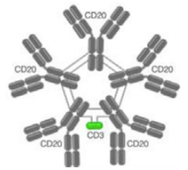
- **Immunotherapy**
  - ***Bispecific MoAb***
  - ***CAR-T***

Bispecific MoAb in NHL



IgG-like Bispecific antibody

Anti-CD20xCD3 BsAb have demonstrated remarkable single-agent activity in patients with heavily pretreated B-NHL with a manageable toxicity profile dominated by T-cell overactivation syndromes

Product name	Schematic depiction	Format
Mosunetuzumab[18]		IgG1
Glofitamab[15]		IgG1
Epcoritamab[16]		IgG1
Odronexamab[17]		IgG4
Plamotamab[90]		IgG1
IgM 2323[19]		IgM

Falchi Blood 2023

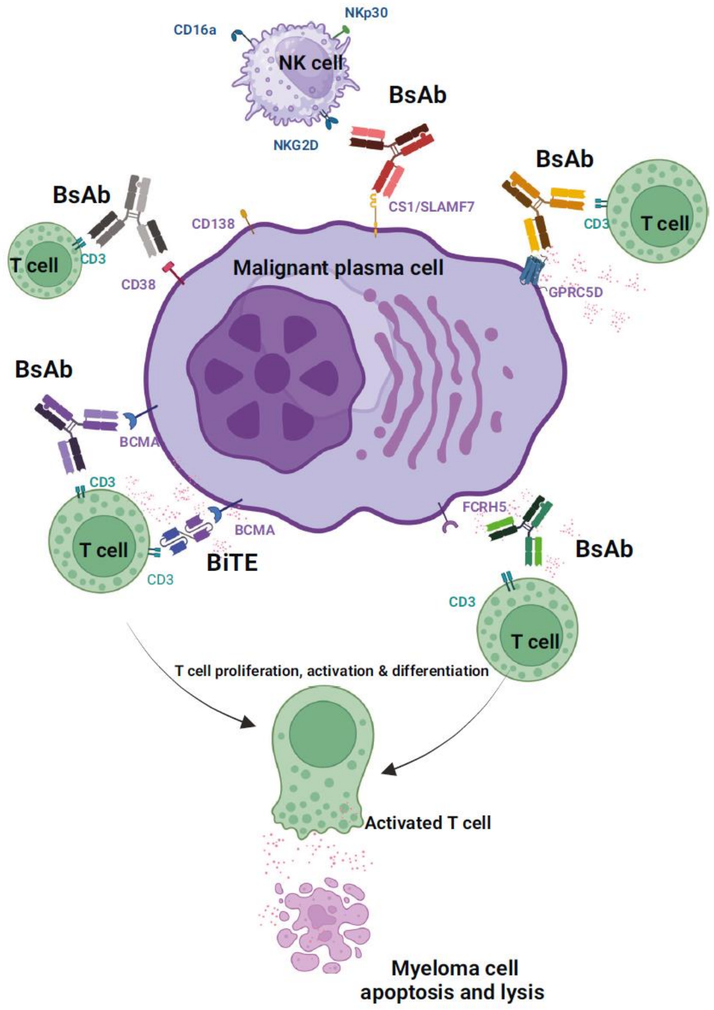
Summary of MoAb toxicity in NHL

Bispecific Antibody	CRS		ICANS		Infection		Fever/Pyrexia		Fatigue	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Blinatumomab [29]	0	0	NR	NR	NR	NR	43.5	4.3	26.1	0
AZD0486 [30]	48	0	27	9.7	NR	NR	NR	NR	NR	NR
Epcoritamab [37–42]	46.4	2.3	2.5	0	41.6	14.6	31.8	0	25	1.9
Plamotamab [43]	72.2	0	NR	NR	NR	NR	38.9	NR	NR	NR
GB261 [44]	12.8	0	0	0	NR	NR	NR	NR	NR	NR
Mosunetuzumab [45–47]	39.4	2.5	4.9	1.6	46.8	15.1	20	0.9	46.7	6.7

The median of any grade infection rates ranged from 41.6% to 49%, while the median grade ≥3 infection rates ranged from 14.6% to 23%

Bayly-McCredie Int J Mol Sci 2024

Bispecific MoAb in MM



Devasia Blood Cancer J 2024

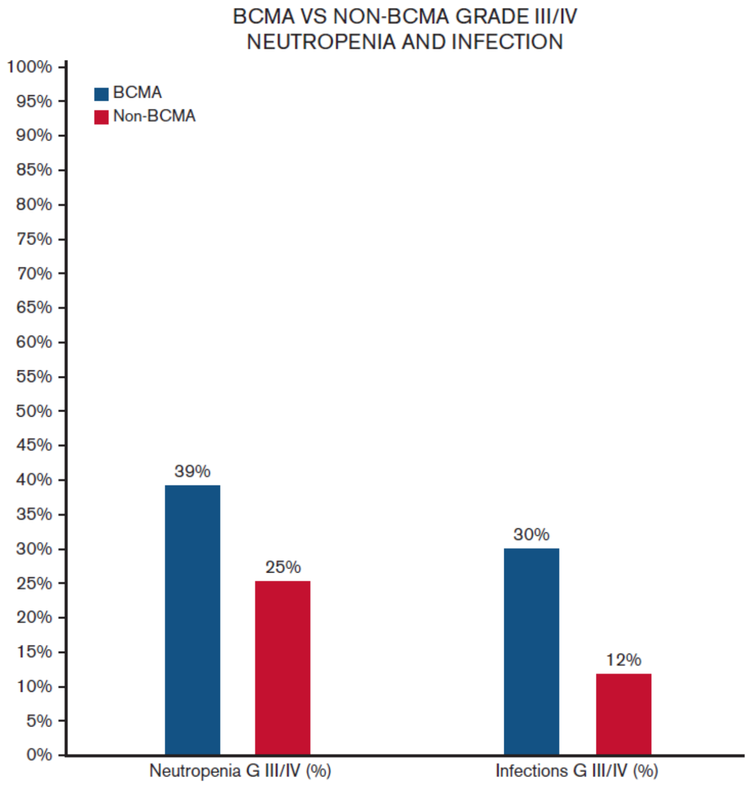
- **BCMA** is a type 3 transmembrane domain protein of the tumour necrosis factor receptor (TNFRSF17) superfamily that is expressed on both **normal and malignant plasma cells** at high levels that makes it an ideal target antigen for myeloma therapy
- Along with its ligands B cell activator of the TNF family (BAFF) and a proliferation inducing ligand (APRIL), it delivers pro-survival cell signals that **regulates B cell proliferation, maturation, survival** as well as differentiation into plasma cell

- **GPRC5D** is a transmembrane receptor protein, encoded by the GPRC5D gene on chromosome 12p and is highly expressed on surface of **malignant plasma cells**, however**, its functions remains unknown**

Bispecific MoAbs in MM: infections

BsAb	Infections %	Infections grade ≥3, %	Hypogammaglobulinemia %	COVID-19 %	CMV %	PJP %	PML %
Talquetamab 405 μg	47	7	87	13	0	NA	NA
Talquetamab 800 μg	34	7	71	2	0	NA	NA
IV talquetamab	NA	NA	NA	NA	NA	NA	NA
Teclistamab	76.4	44.8	74.5	17.6 (12.1 grade ≥3; 11 deaths)	NA	NA	0.01
Elranatamab[38,39]	73.6	26.4	NA	25.3	NA	NA	NA
Cevostamab	42.5	18.8	NA	NA	NA	NA	NA

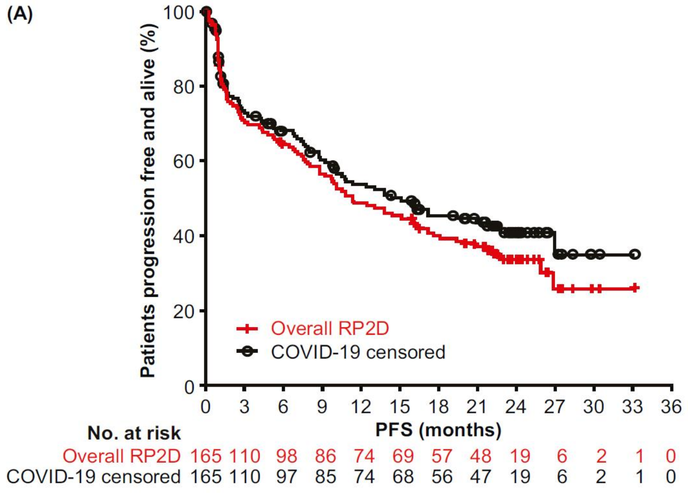
Liu Haematologica 2024

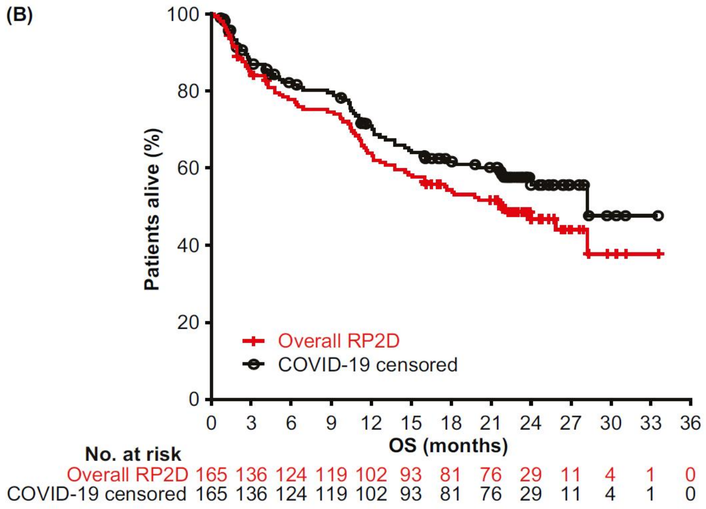


Of the patients treated with BsAbs, half developed an infection, and a quarter developed grade III/IV infections

Mazahreh Blood Adv 2023

MajesTEC-1 and infections

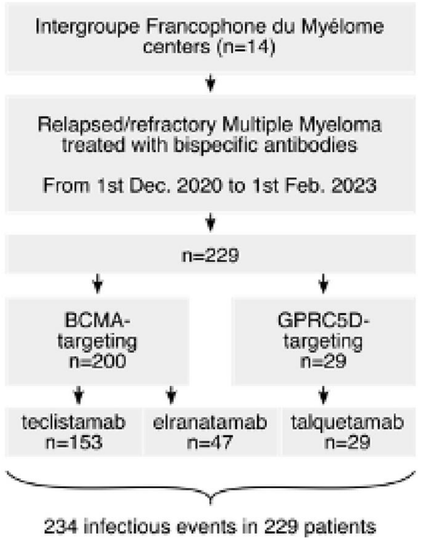


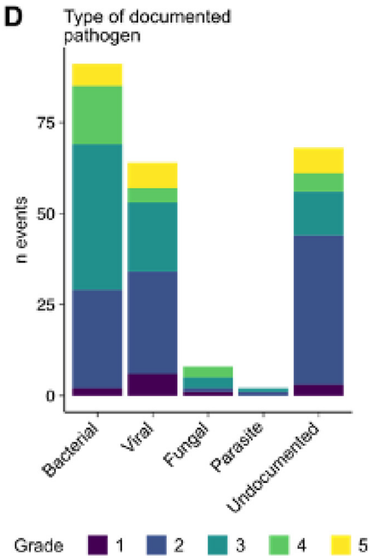


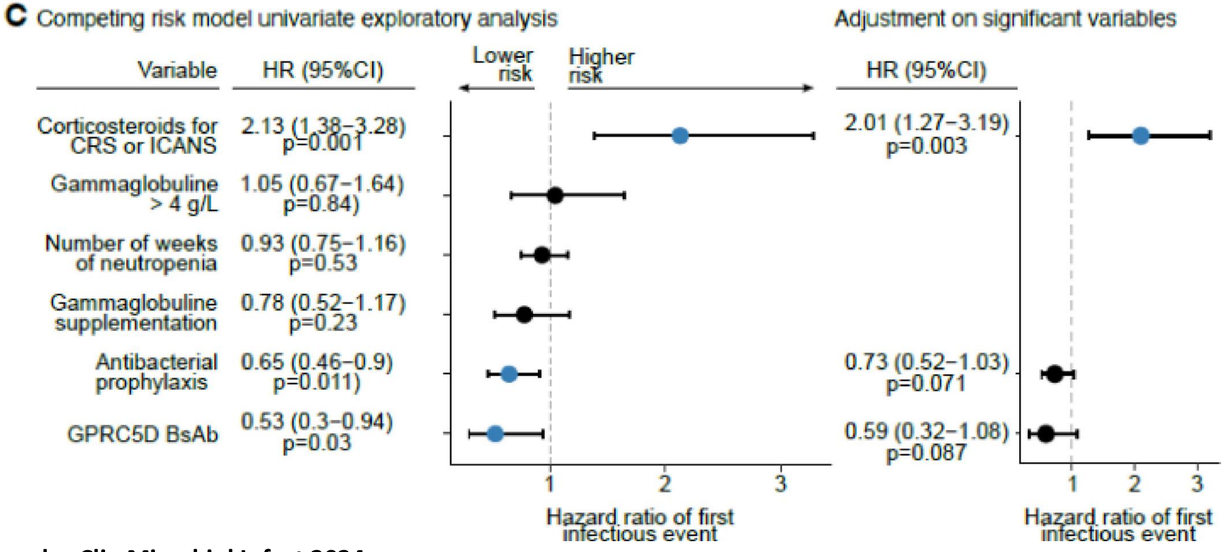
- **Recruitment for the phase 1/2 MajesTEC-1 study** evaluating teclistamab **ran concurrently with the start of the COVID-19 pandemic**
- **The majority of the 165 patients** in the teclistamab recommended phase 2 dose (RP2D) cohort were **enrolled between March 2020 and March 2021** (n = 151; 91.5%), overlapping with **peak infection** and death rates worldwide
- During the study, **48 patients (29.1%) had a COVID-19** infection (grade 3/4 in 35 patients [21.2%]) and **18 patients (10.9%) died from COVID-19**

Van de Donk Blood Cancer J 2024

Retrospective, multicentre study



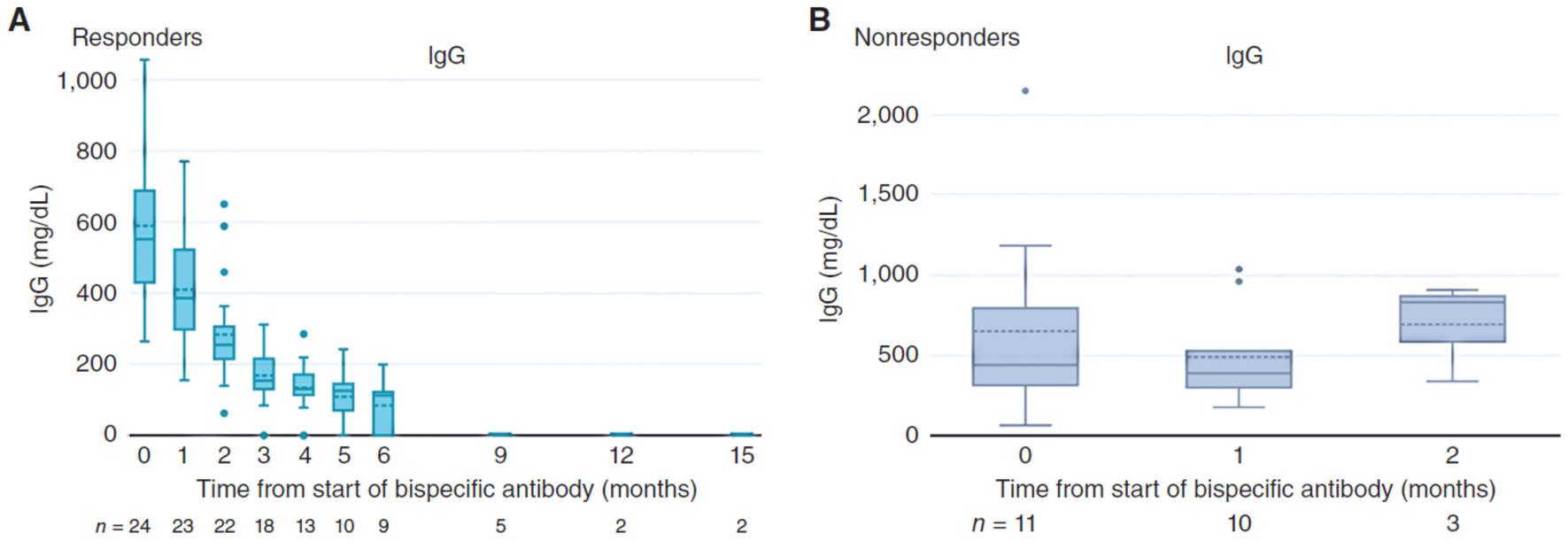




Jourdes Clin Microbiol Infect 2024

- Among the 229 patients, 142 (**62%**) presented **at least one infection** affecting patient management with a median time from BsAb initiation of 49 days (IQR: 17-112)
- 133 (**61%**) infections in patients with **hypogammaglobulinaemia <400 mg/dL** at the time of infection and 50 (21%) in patients under immunoglobulin substitution
- Global cumulative incidence of the first infection was 70% in all patients, **73%** in patients treated with **BCMA-targeting**, and **51%** with **GPRC5D-targeting BsAb**
- All **grade 4-5 or requiring ICU admission infections** involved patients undergoing **BCMA-targeting BsAb**

Hypogammaglobulinemia and anti BCMA MoAbs



- Retrospective study
- Among 37 patients, 15 (**41%**) experienced a **grade 3–5 infection**, with two infection-related deaths during deep remissions
- Most (84%) infections occurred during **disease remissions**
- The cumulative probability of grade 3–5 infection increased over time with **no plateau**

Lancman Blood Cancer Disc 2023

Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in multiple myeloma: a consensus report of the European Myeloma Network

Lancet Oncol 2023; 24: e255–69

Heinz Ludwig, Evangelos Terpos, Niels van de Donk, Maria-Victoria Mateos, Philippe Moreau, Melitios-Athanasios Dimopoulos, Michel Delforge, Paula Rodriguez-Otero, Jesús San-Miguel, Kwee Yong, Francesca Gay, Hermann Einsele, Roberto Mina, Jo Caers, Christoph Driessen, Pellegrino Musto, Sonja Zweegman, Monika Engelhardt, Gordon Cook, Katja Weisel, Annemiek Broijl, Meral Beksac, Jelena Bila, Fredrik Schjesvold, Michele Cavo, Roman Hajek, Cyrille Touzeau, Mario Boccadoro, Pieter Sonneveld

	Teclistamab (MajesTEC-1)[2]	Talquetamab (MonumenTAL-1)[3]	Elranatamab (MagnetisMM-1)[4]	Elranatamab (MagnetisMM-3)[5]	Linvoseltamab[6]	ABBV-383 (formerly TNB-383B)[7]	Alnuctamab[8]	Forimtamig (formerly RG6234)[9]	Cevostamab (NCT03275103)[10]
Target structure	BCMA and CD3	GPRC5D and CD3	BCMA and CD3	BCMA and CD3	BCMA and CD3	BCMA and CD3	BCMA and CD3	GPRC5D and CD3	FcRH5 and CD3
Infections grade 1–4	76·4% (44·8% grade ≥3)	57·3% (16·8%, grade ≥3)	27·3%, grade ≥3	66·7% (35·0%, grade ≥3)	54·0% (29·0%, grade ≥3)	41·0%	34·0% (9·0%, grade ≥3)	60·8% (21·5%, grade ≥3)	42·5% (18·8% grade ≥3)

iv Ig supplementation if IgG<400 mg/dl

International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations for optimal use of T-cell-engaging bispecific antibodies in multiple myeloma

www.thelancet.com/oncology Vol 25 May 2024

*Paula Rodriguez-Otero, Saad Usmani, Adam D Cohen, Niels W C J van de Donk, Xavier Leleu, Jaime Gállego Pérez-Larraya, Salomon Manier, Ajay K Nooka, Maria Victoria Mateos, Hermann Einsele, Monique Minnema, Michele Cavo, Benjamin A Derman, Noemi Puig, Francesca Gay, P Joy Ho, Wee-Joo Chng, Efstathios Kastritis, Gösta Gahrton, Katja Weisel, Chandramouli Nagarajan, Fredik Schjesvold, Joseph Mikhael, Luciano Costa, Noopur S Raje, Elena Zamagni, Roman Hájek, Niels Weinhold, Kwee Yong, Jing Christine Ye, Surbhi Sidana, Giampaolo Merlini, Tom Martin, Yi Lin, Ajai Chari, Rakesh Popat, Jonathan L Kaufman, on behalf of the International Myeloma Working Group**

- Ongoing T-cell activation, T-cell exhaustion, or treatment-induced depletion of some T-cell populations in addition to hypogammaglobinaemia and neutropenia might partially explain the high risk of infections seen in patients treated with bispecific antibodies

- For non-BCMA bispecific Ab, new onset of grade 3–4 infections generally occurred in the first 100 days of therapy

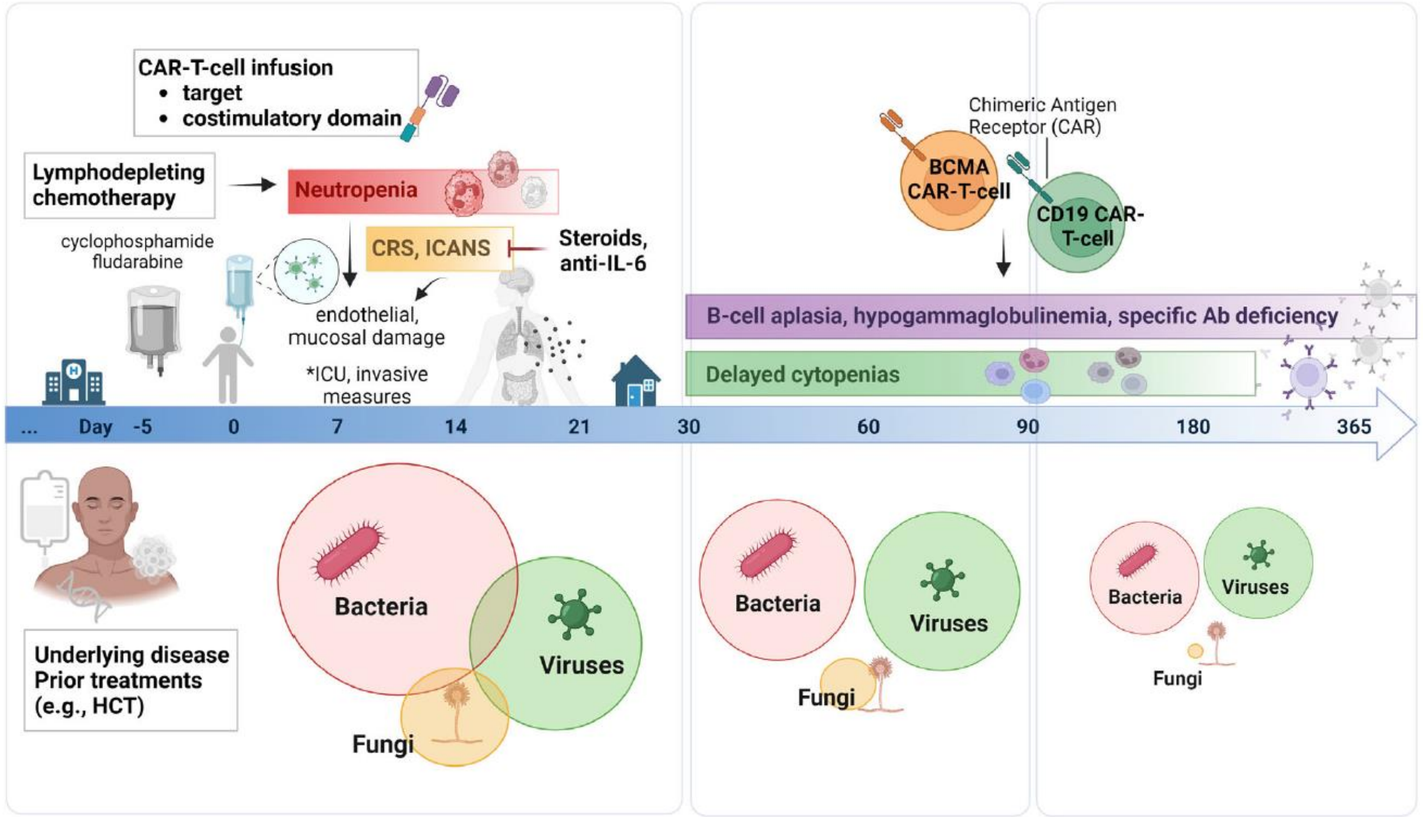
- For BCMA bispecific antibodies the incidence is more or less constant throughout therapy

	Agent or agents	Timing	Additional comments and recommendations
Antiviral: herpes simplex virus or varicella zoster virus	Aciclovir or valacyclovir	Throughout treatment	Continue for 3 months off treatment or until CD4 >200/μL
Pneumocystis	Trimethoprim/sulfamethoxazole, atovaquone	Throughout treatment	Continue until CD4 cell count >200/μL
Antibacterial	Local guidelines or quinolone	Neutropenia	Bacterial infection highest in first few cycles during neutropenia or if prolonged steroids needed
Antifungal	Local guidelines or azole	Neutropenia	Fungal infection risk low, consider during prolonged neutropenia or steroid use
Other viral; cytomegalovirus, hepatitis B virus	Entecavir for those at risk of reactivation	Throughout treatment	Cytomegalovirus PCR at start and if positive consider monitoring; local guidelines for monitoring versus preemptive treatment
Polymicrobial	Intravenous immunoglobulin	For IgG concentration <400 mg/dL	Hypogammaglobulinaemia is common throughout treatment; continue even off therapy for IgG concentrations <400 mg/dL

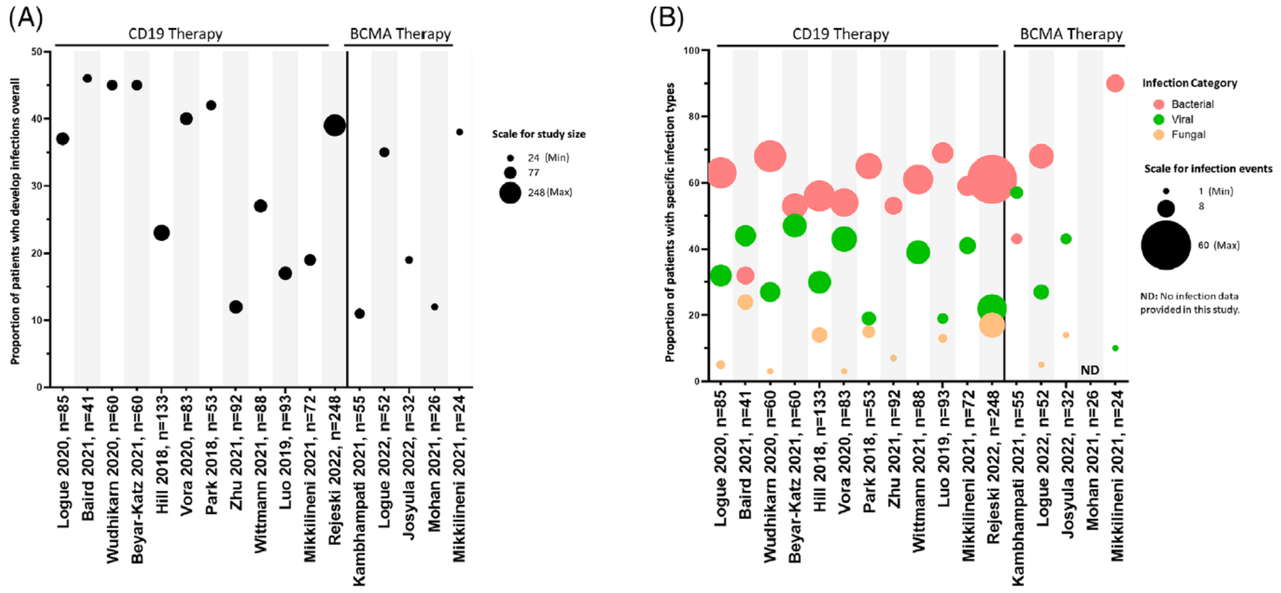
Table 4: **Infection prevention with bispecific antibody therapy**

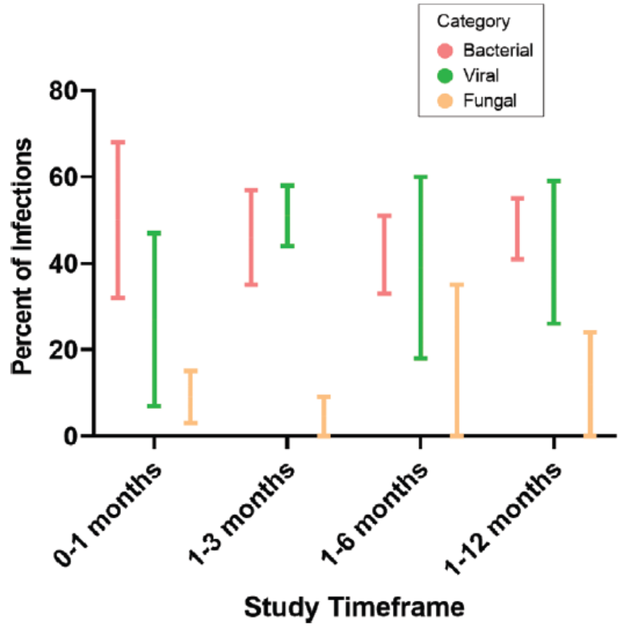
Infection susceptibility for CAR-T cell therapy

Kampouri Transpl Infect Dis 2023



Bacterial and viral infections predominate





Timeframe	Bacterial cause	Viral cause	Fungal cause	References
0–1 month	32%–68%	7%–47%	3%–15%	35-38,40,49, 50,57,59,79
1–3 months	35%–57%	44%–58%	0%–9%	35,38,59
1–6 months	33%–51%	18%–60%	0%–35%	37,46,49
1–12 months	41%–55%	26%–59%	0%–24%	40,49,59

Kampouri Transpl Infect Dis 2023

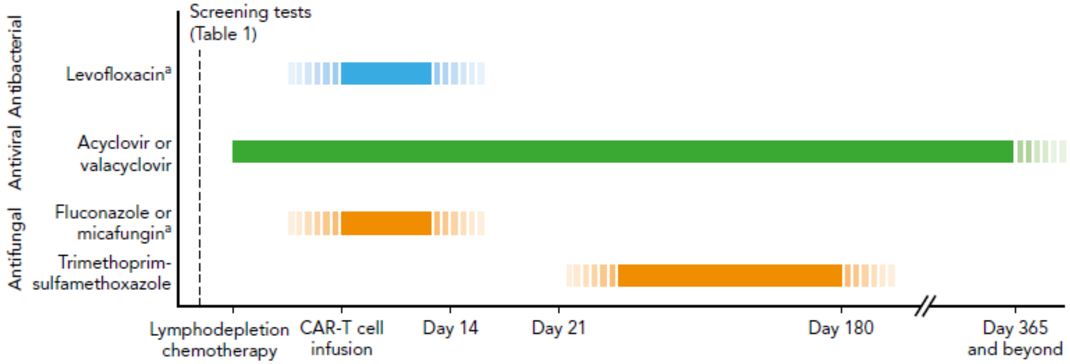
CAR-T cell therapy – timing of infections

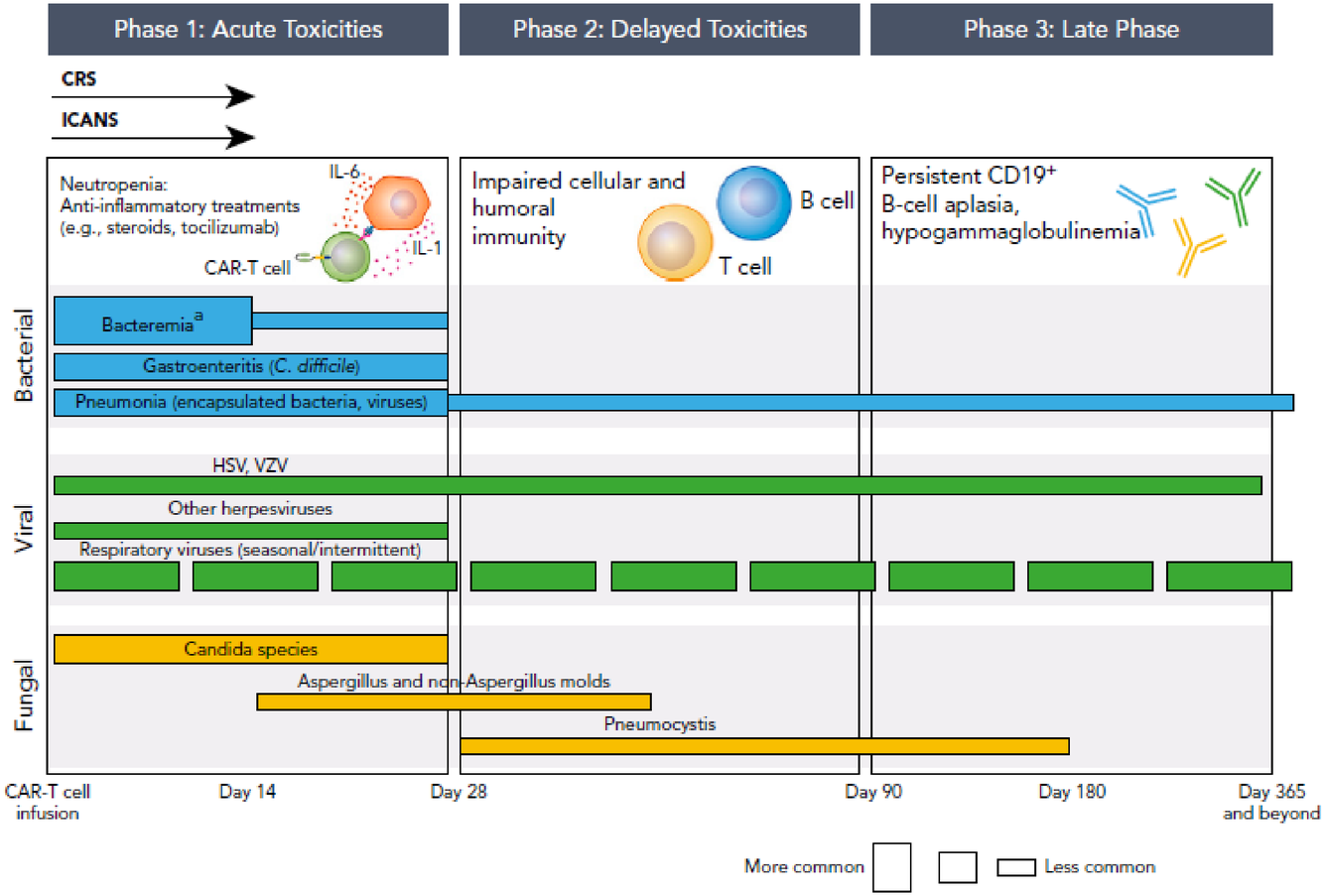
Bacterial
- Early 17-30%
- Late 7-16%

Viral 8-28%

Fungal 2-8%

Prophylaxis





Gudiol Lancet Haematol 2021
Hill Blood 2018

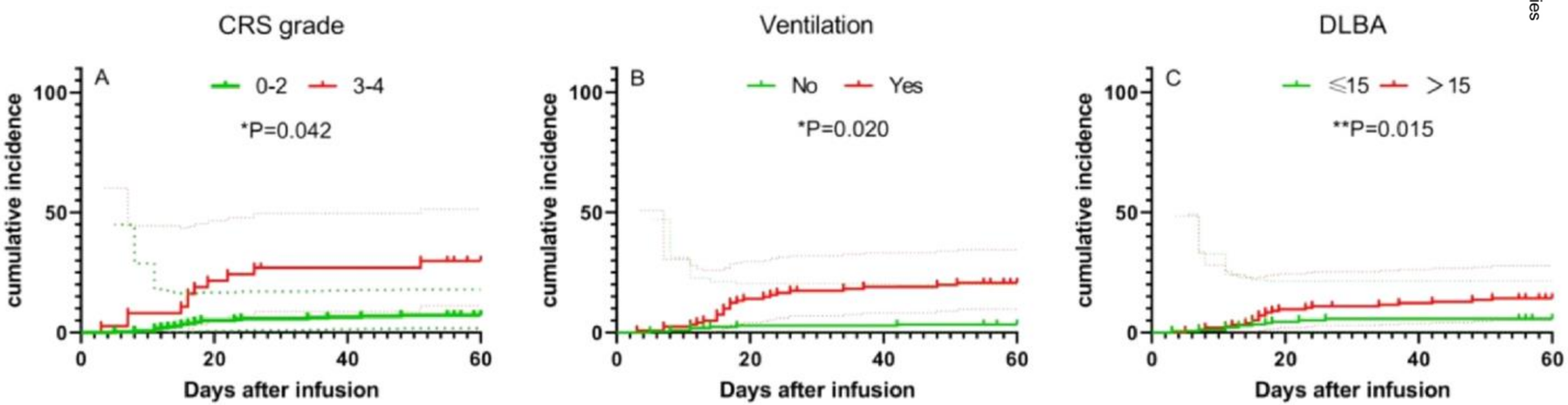
Prolonged duration of lymphocyte deficiency, high-grade CRS, and ventilation are linked to fungal breakthrough in patients with hematologic malignancies 60 days after CAR-T infusion: A single center case-control study

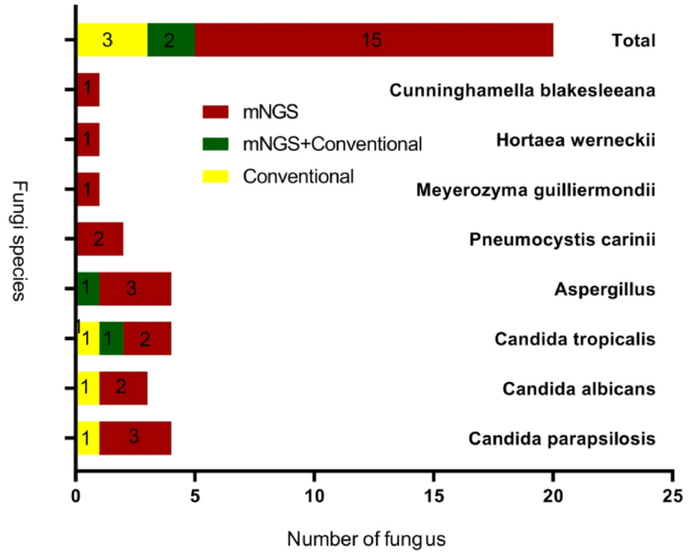
Journal of Infection and Public Health 15 (2022) 1521–1530

Jian Yang [a,b], Jinwen Zhang [a], Jia Wei [c], Guangjie Wu [a], Jianxin Song [d], Dong Liu [a,1,*], Yan He [a,2,*]

- Case-control study
- June 2018-December 2020
- 330 pts
- 32 IFI

IFI was not a risk factor for death within 1 year of CAR-T therapy





Cumulative incidence curves of time-to-first IFIs

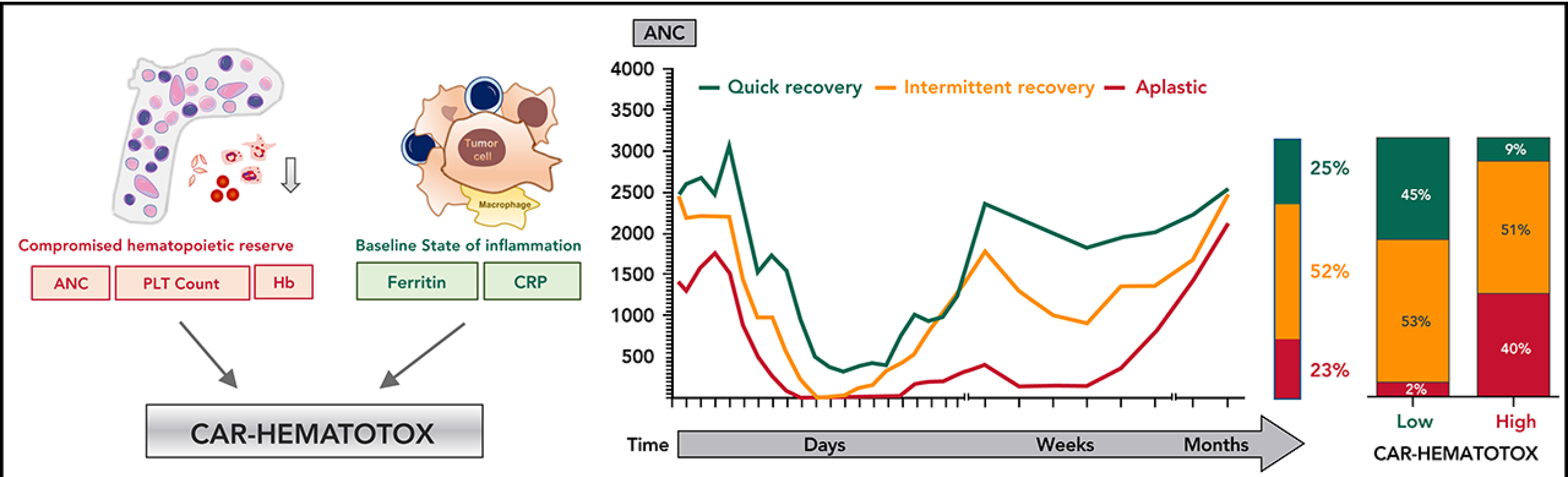
CAR-T HEMATOTOX

blood® 16 DECEMBER 2021 | VOLUME 138, NUMBER 24

KEY POINTS

- **Baseline cytopenia and inflammatory state are associated with prolonged neutropenia after CAR T-cell therapy in the real-world setting.**
- **The CAR-HEMATOTOX represents an easy-to-use risk-stratification tool that is helpful in ruling out patients at risk of hematotoxicity.**

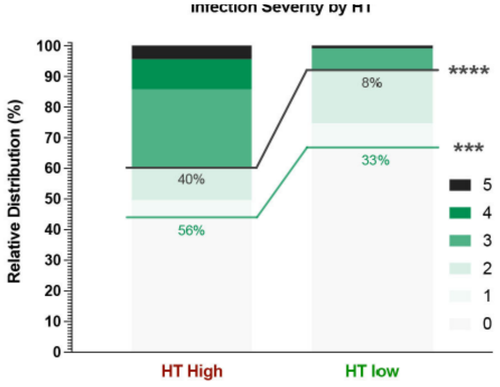
Baseline Features	0 Point	1 Point	2 Points
Platelet Count	> 175,000/µl	75,000 – 175,000/µl	< 75,000/µl
Absolute Neutrophil Count (ANC)	> 1200/µl	< 1200/µl	-
Hemoglobin	> 9.0 g/dl	< 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	> 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650 – 2000 ng/ml	> 2000 ng/ml
Low: 0-1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

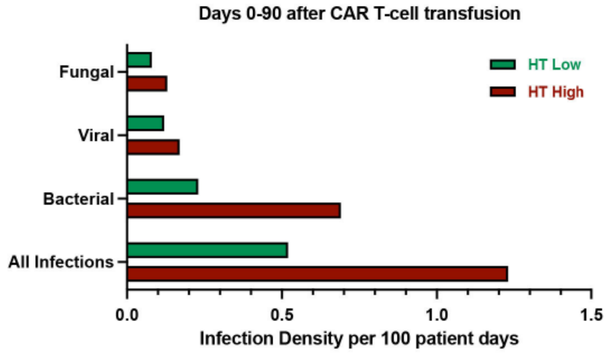


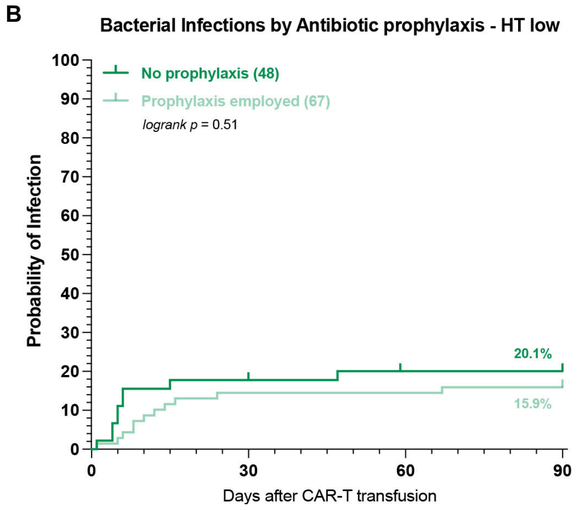
The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CAR-T in R/R LBCL

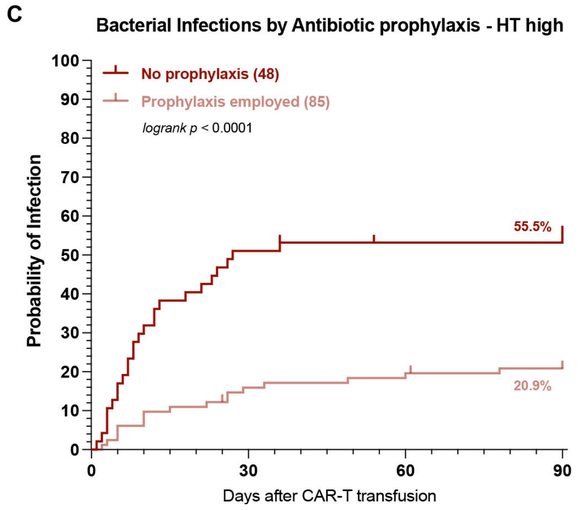
Rejeski K, *et al. J Immunother Cancer* 2022;**10**:e004475.

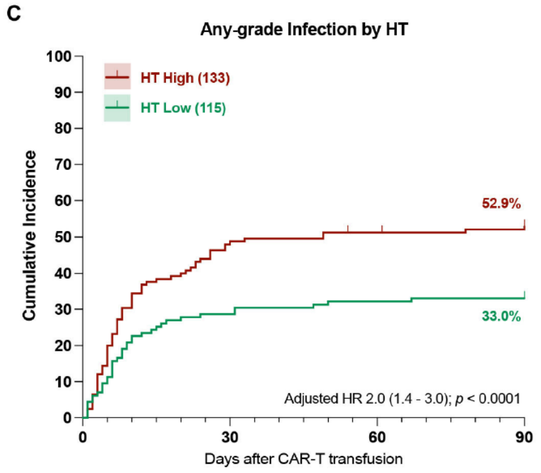
Kai Rejeski ,[1,2,3] Ariel Perez,[4,5] Gloria Iacoboni,[6] Olaf Penack,[7,8] Veit Bücklein,[1,2] Liv Jentzsch,[9] Dimitrios Mougiakakos,[10] Grace Johnson,[11] Brian Arciola,[11] Cecilia Carpio,[6] Viktoria Blumenberg,[1,2] Eva Hoster,[12] Lars Bullinger,[7,8] Frederick L Locke,[4] Michael von Bergwelt-Baildon,[1,3] Andreas Mackensen,[10]

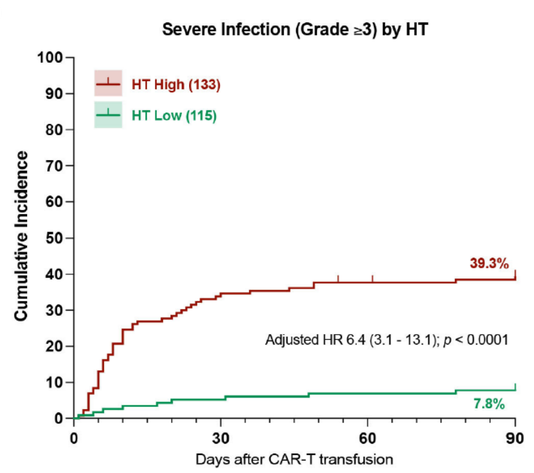










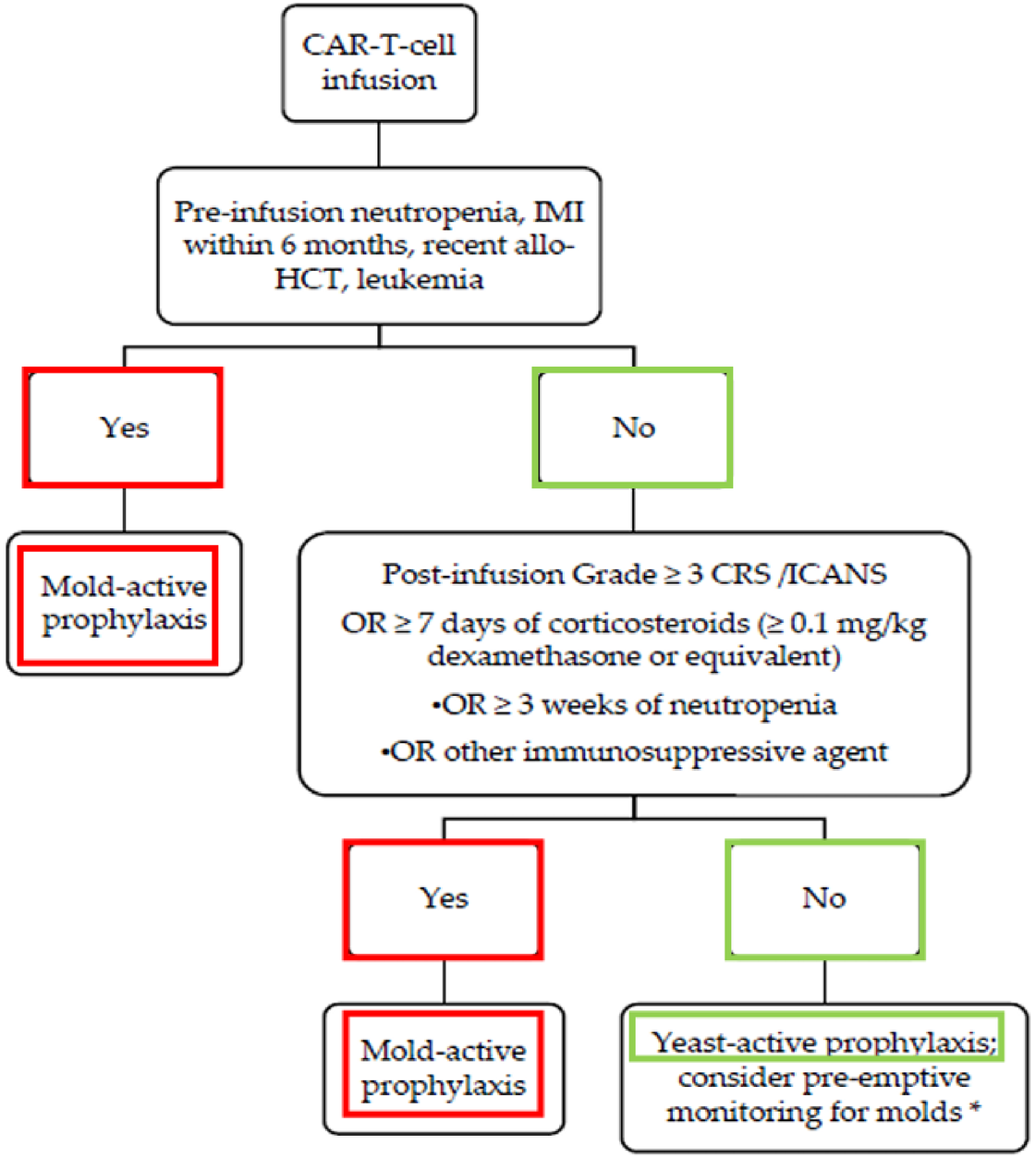


- Infection risk was increased by prolonged neutropenia (≥14 days) and corticosteroid use (≥9 days), and decreased with fluoroquinolone prophylaxis

- Multicenter retrospective analysis
- 248 patients CD19 CAR-T for relapsed/refractory large B-cell lymphoma
- Early infection events (days 0–90) and clinical outcomes

AntiCD19 CART cells

Panel proposes to **endorse these recommendations (B II)**



Garner et al, J of Fungi 2021

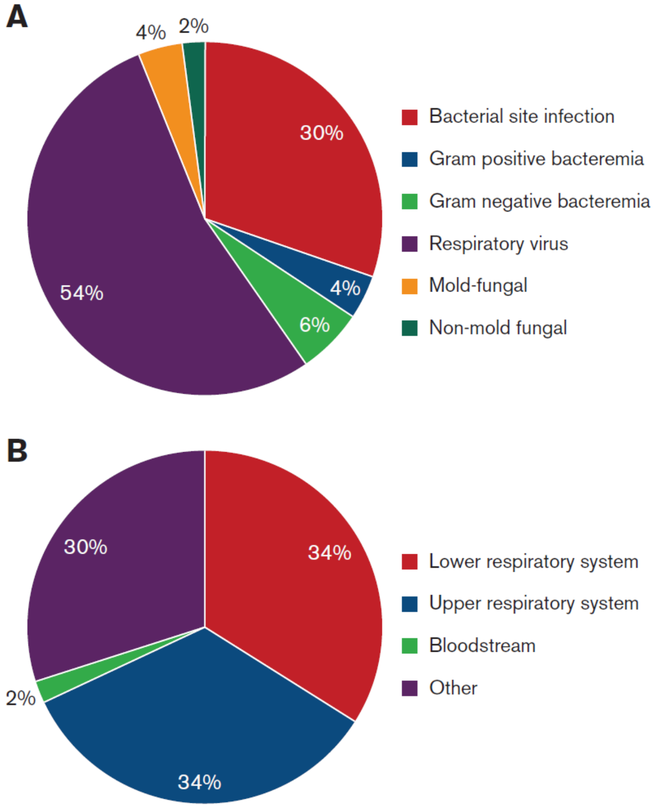
Infectious complications in patients with relapsed refractory multiple myeloma after BCMA CAR T-cell therapy

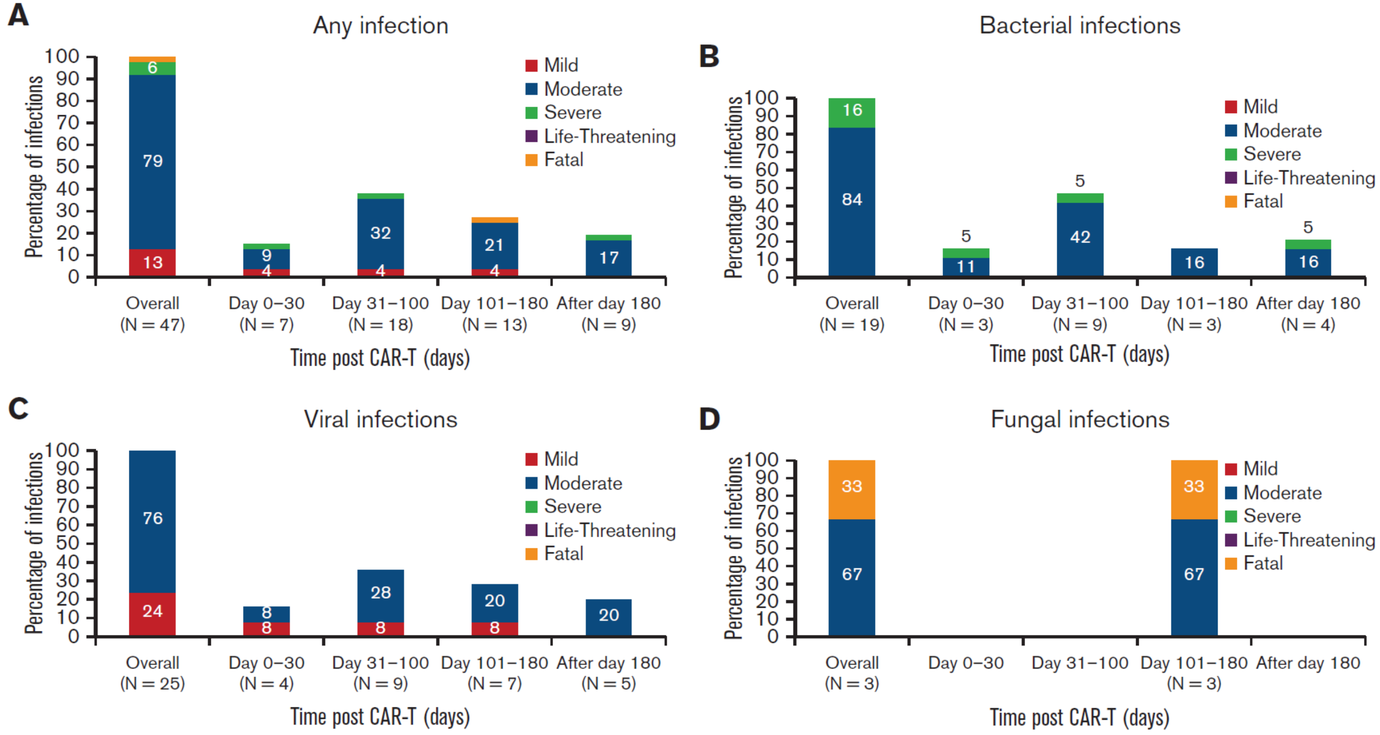
1-y restrospecive study

blood advances
12 APRIL 2022 • VOLUME 6, NUMBER 7

Swetha Kambhampati,[1,2] Ying Sheng,[3] Chiung-Yu Huang,[3] Sophia Bylsma,[2] Mimi Lo,[4] Vanessa Kennedy,[1,2] Kelsey Natsuhara,[5] Thomas Martin,[1,2] Jeffrey Wolf,[1,2] Nina Shah,[1,2] and Sandy W. Wong[1,2]

[1]Division of Hematology/Oncology, Department of Medicine; [2]University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center; [3]Department of Epidemiology and Biostatistics; [4]Department of Pharmacy and [5]Department of Medicine, UCSF Medical Center, San Francisco, CA

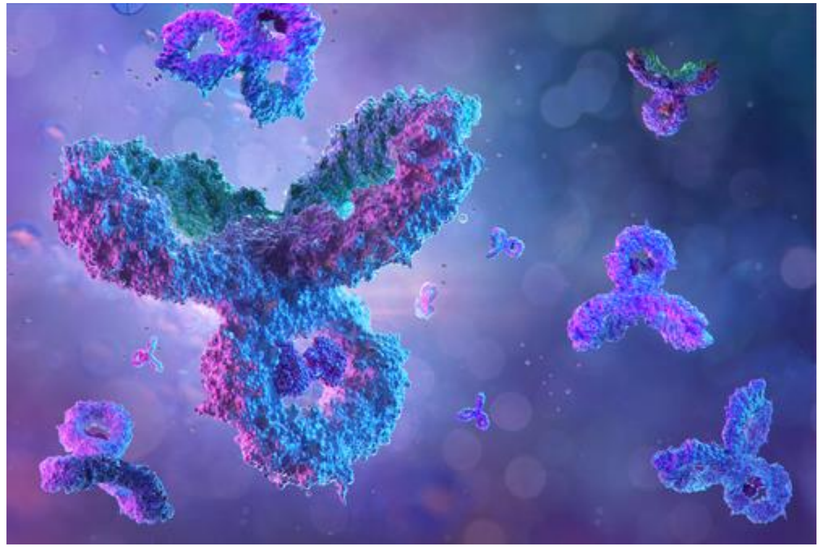


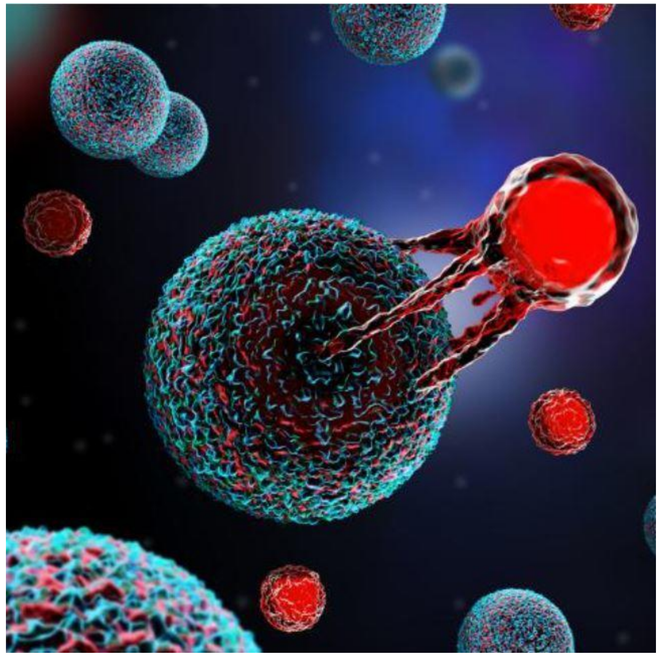


Key Points

- Forty percent bacterial, 53% viral, and 6% fungal infections in 29 of 55 patients with multiple myeloma were observed after BCMA CAR-T.
- Most infections after BCMA CAR-T were mild-moderate and involved upper or lower respiratory system.

Infections in bispecific MoAbs and CAR-T cells: the winner is..?



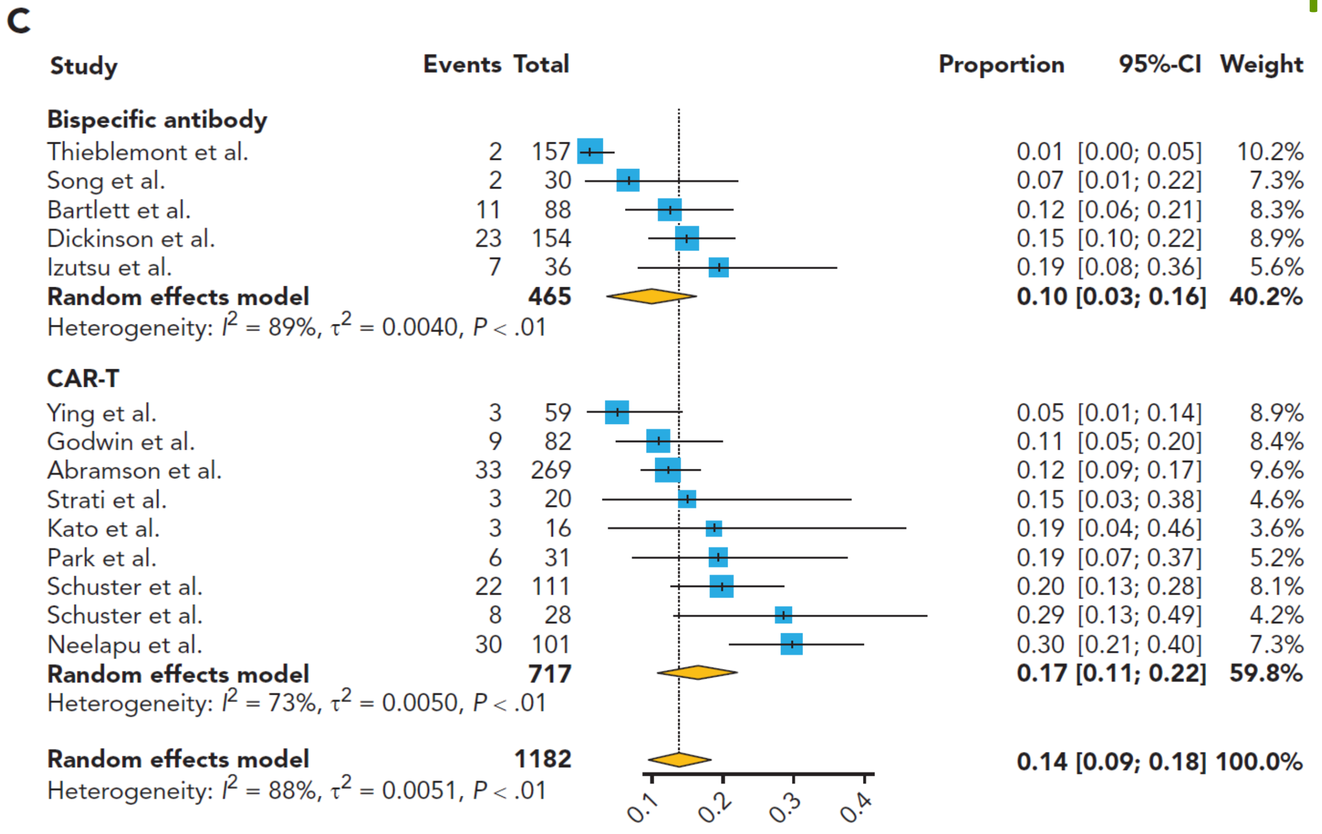


Grade ≥3infections: bispecific MoAb vs CAR-T (lymphoma patients)

KEY POINTS

- **CAR T-cell therapy demonstrates superior efficacy to bispecific antibody in DLBCL treatment, with higher CR rates.**
- **CAR T-cell therapy exhibits higher incidence of grade ≥3 adverse events than bispecific antibody.**

Infections



Kim Blood 2024

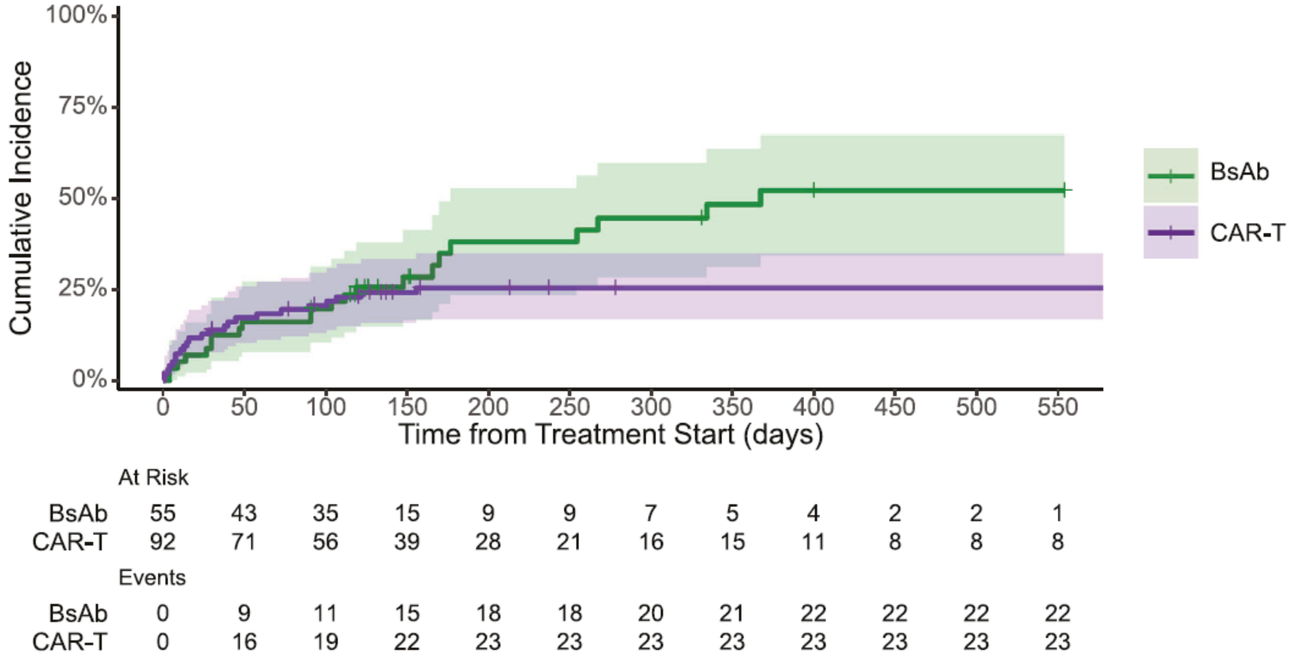
ARTICLE OPEN

Check for updates

Comparison of infectious complications with BCMA-directed therapies in multiple myeloma

Blood Cancer Journal (2024)14:88 ; https://doi.org/10.1038/s41408-024-01043-5

Karthik Nath[1,9], Tala Shekarkhand[2,9], David Nemirovsky[3], Andriy Derkach[3], Bruno Almeida Costa[4,5], Noriko Nishimura[2,6], Tasmin Farzana[1], Colin Rueda[2], David J. Chung[1,6,7], Heather J. Landau[1,6,7], Oscar B. Lahoud[1,6,7], Michael Scordo[1,6,7], Gunjan L. Shah[1,6,7], Hani Hassoun[2,7], Kylee Maclachlan[2,7], Neha Korde[2,7], Urvi A. Shah[2,7], Carlyn Rose Tan[2,7], Malin Hultcrantz[2,7], Sergio A. Giralt[1,6,7], Saad Z. Usmani[1,2,6,7], Zainab Shahid[7,8], Sham Mailankody[1,2,7,10]✉ and Alexander M. Lesokhin[1,2,7,10]✉

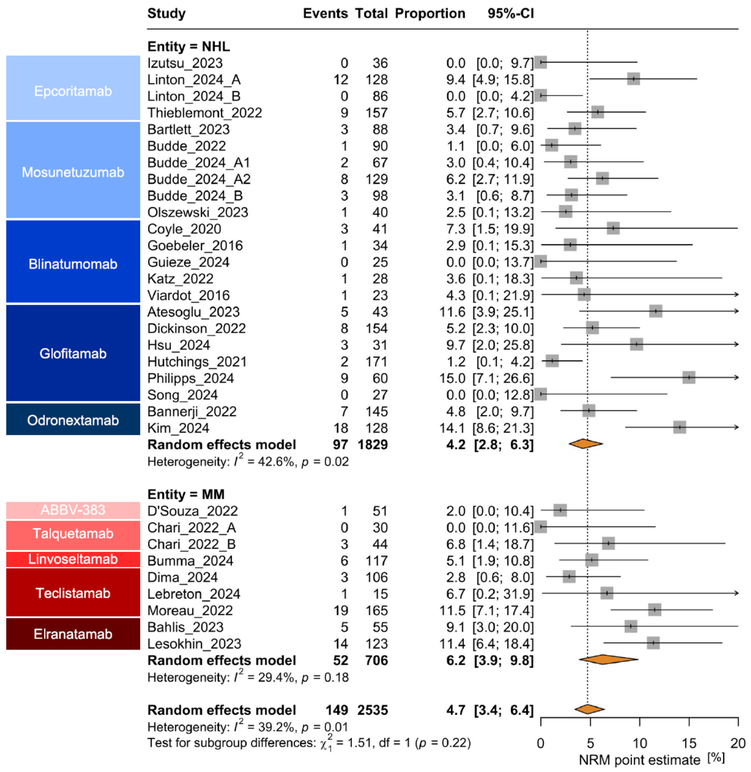


	At Risk											
BsAb	55	43	35	15	9	9	7	5	4	2	2	1
CAR-T	92	71	56	39	28	21	16	15	11	8	8	8
	Events											
BsAb	0	9	11	15	18	18	20	21	22	22	22	22
CAR-T	0	16	19	22	23	23	23	23	23	23	23	23

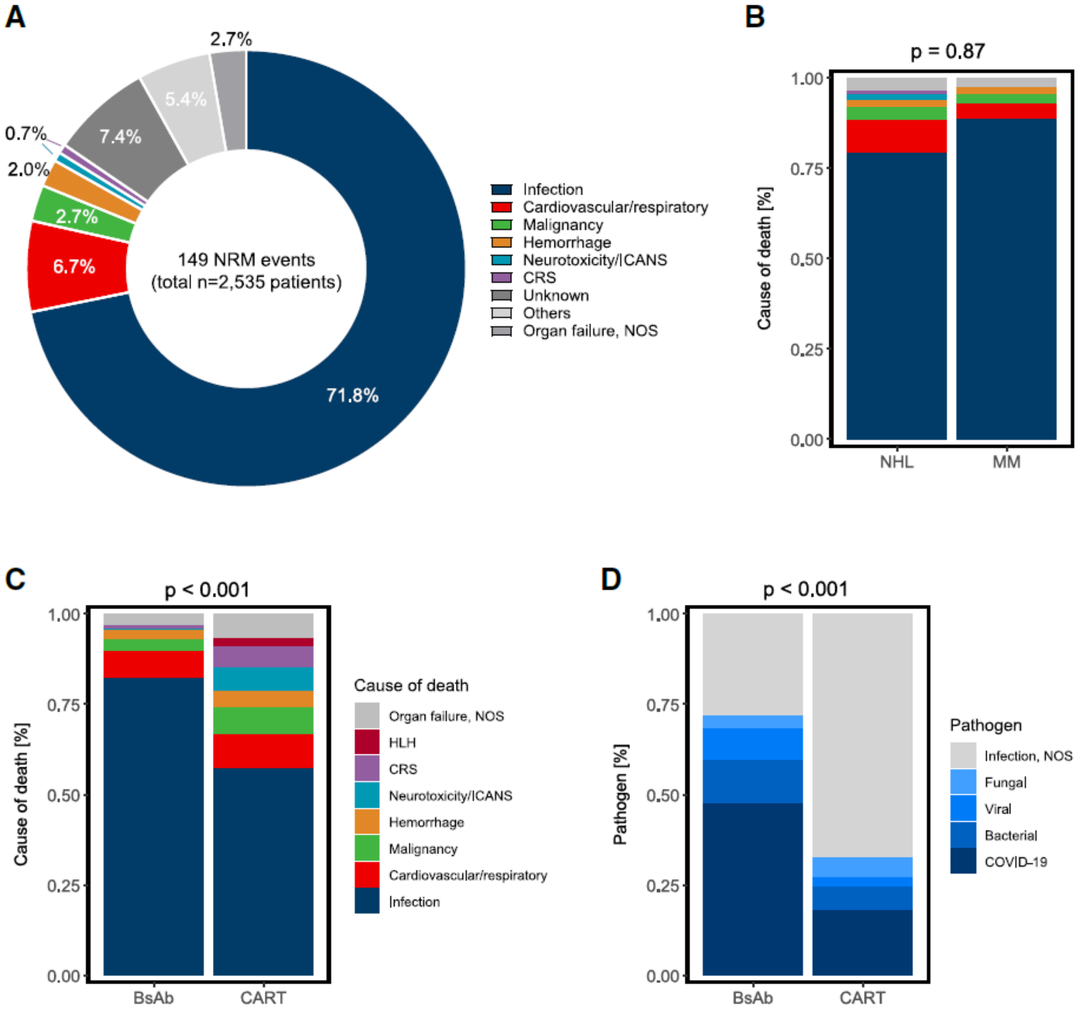
«…the incidence of severe (grade ≥3) infections was numerically lower with CAR-T with 26% of patients experiencing severe infections compared to 40% with BsAb (hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.32–1.04, P = 0.067)»

Higher and more persistent risk of severe infections with BsAb

Non-relapse mortality in Bispecific MoAbs: comparison with CAR-T



- Overall **NRM 4.7%**
- **NHL: 4.2%, MM: 6.2%**
- In **NHL increased NRM in real-world** studies compared to clinical trials
- For **MM**, an **association between NRM and higher response rates and longer follow-up** was noted
- **Infections** were the **leading cause of NRM**



Tix Mol Ther 2025

Conclusions

- Mind the **immune sequelae** of targeted therapies (**off-target effects** can impact on **innate or adaptive immunity**)
- **Age, type of hematological disease**, as well as **treatment delivered**, should be considered for risk of infections
- Fungal infections during **BTK-i** treatment, particularly in association with **steroids**, although **AF prophylaxys is not recommended**
- **Persistent risk of infections** with **bispecific MoAB**, particularly in **MM** patients; Ig supplementation
- **CAR-T hematotox** to predict the severity of infections in **antiCD19 CAR-T** cell therapy