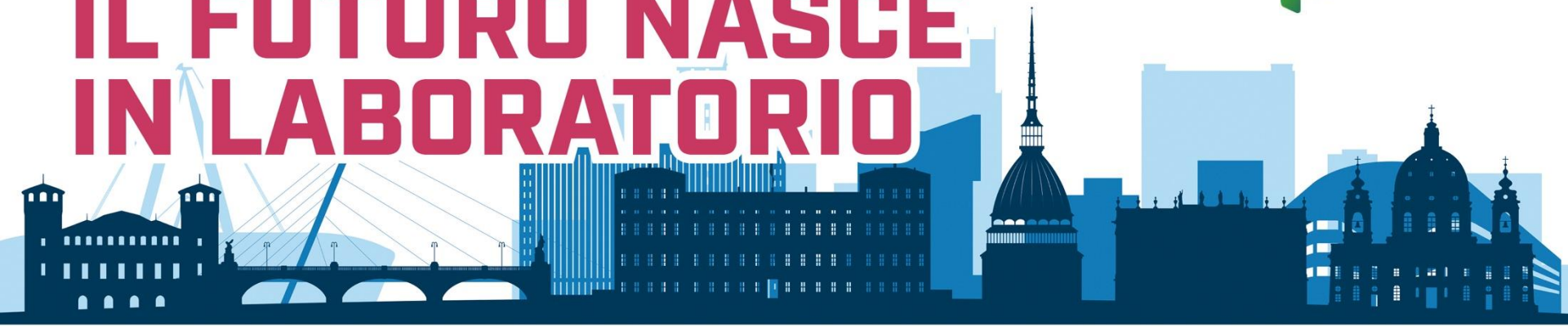
REGIONALE SIES – Delegazione Piemonte

YOUNG SCIENCE FORUM: IL FUTURO NASCE IN LABORATORIO



DBMSS
Dipartimento di Biotecnologie Molecolari e Scienze per la Salute

Meccanismo d'azione degli anticorpi bispecifici: dalla biologia ai risultati clinici

Simone Ragaini, MD

Department of Molecular Biotechnology and Health Sciences, University of Torino,

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

UNIVERSITÀ DI TORINO

TORINO, ACCADEMIA DI MEDICINA | 4-5 GIUGNO 2026

Disclosures of Simone Ragaini

Company name	Research support	Employee	Consultant	Stockholder	Speakers honoraria	Advisory board	Other
Pierre Fabre					x		
Beigene					x		x
Roche					x		
Novartis					x		
Astrazeneca					x		
Gilead/Kyte							x

Review TRENDS in Biotechnology Vol.22 No.5 May 2004
Full text provided by www.sciencedirect.com SCIENCE DIRECT

A revival of bispecific antibodies

Peter Kufer[1,2], Ralf Lutterbüse[1] and Patrick A. Baeuerle[1]

[1]Micromet AG, Staffelseestr. 2, 81477 Munich, Germany
[2]Institute of Immunology, Goethestr. 31, 80336 Munich, Germany

Bispecs are mostly designed to recruit cytotoxic effector cells of the immune system effectively against pathogenic target cells.

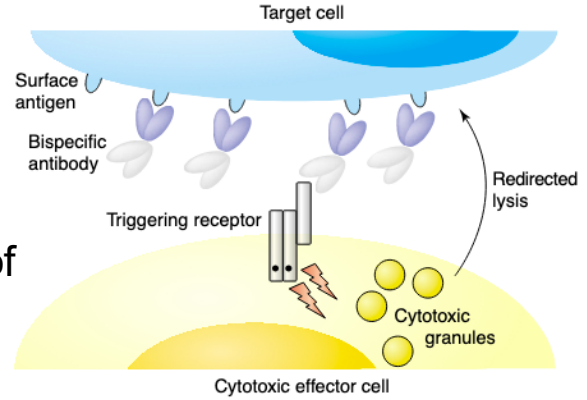
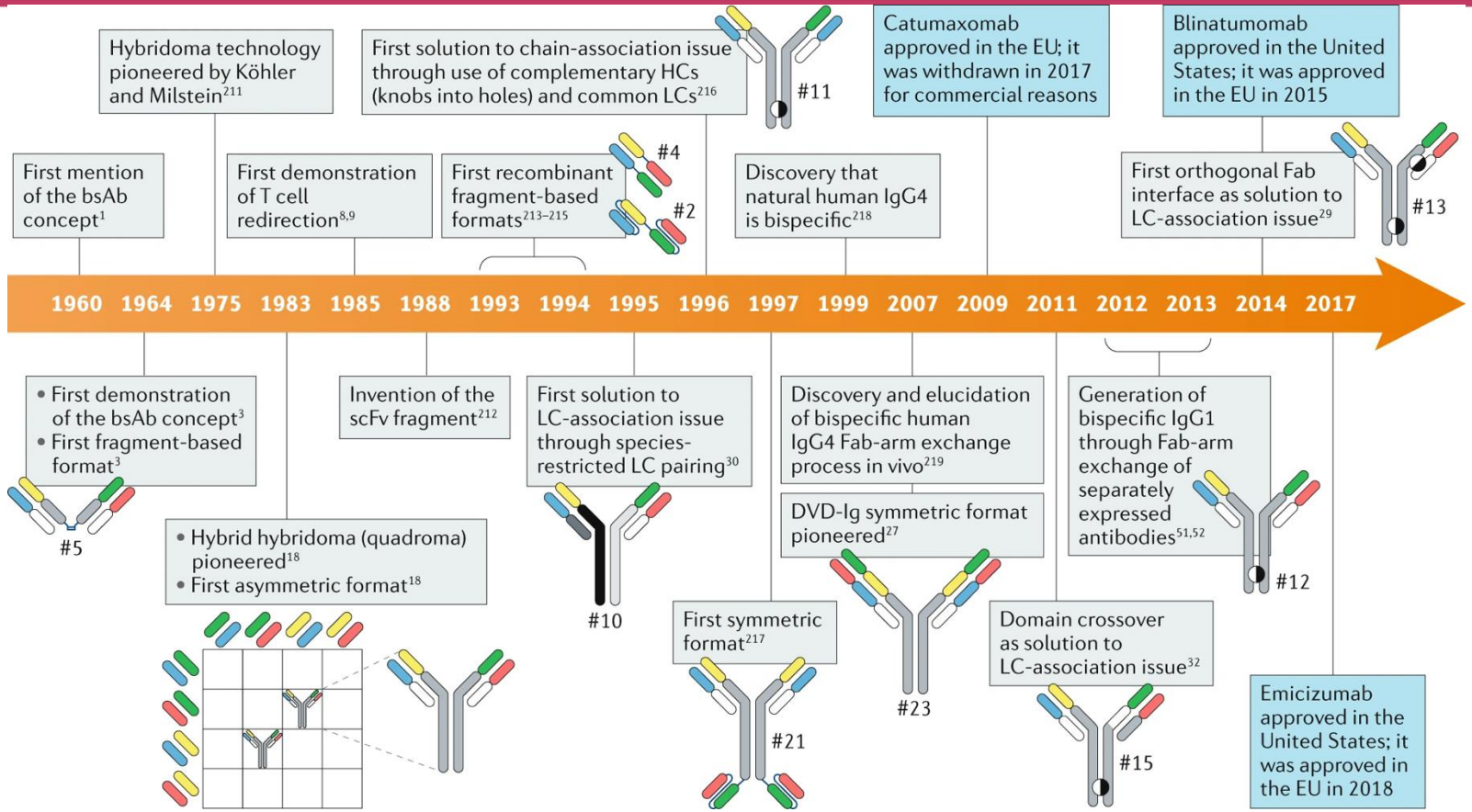


Table 1. Characteristics of bispecific antibodies recruiting cytotoxic effector cells and requirements for redirected target-cell lysis

Triggering molecule	CD64	CD89	CD16	CD3	
Bispecific antibody format	$F(ab')_2$	$F(ab')_2$	Quadroma $F(ab')_2$ Tandem scFv	$F(ab')_2$ Diabody	BiTE
Effector cells	Monocytes and neutrophils		NK cells	T cells	
Requirement of pre- or costimulation	Yes	No	Yes	Yes	No
ED_{50} range [$\mu g\ ml^{-1}$]	0.1–1	0.1–1	0.03–1	0.001–1	10^{-5}–10^{-4}
E:T ratio	≥40:1	100:1–200:1	50:1	≥2:1	≤ 1:10
Refs	[44]	[46]	[49]	[28,57]	[80]


1960
1964
1975
1983
1985
1988
1993
1994
1995
1996
1997
1999
2007
2009
2011
2012
2013
2014
2017
First mention of the bsAb concept[1]
Hybridoma technology pioneered by Köhler and Milstein[211]
First demonstration of T cell redirection[8,9]
First recombinant fragment-based formats[213–215]
#4
#2
First solution to chain-association issue through use of complementary HCs (knobs into holes) and common LCs[216]
#11
Discovery that natural human IgG4 is bispecific[218]
Catumaxomab approved in the EU; it was withdrawn in 2017 for commercial reasons
Blinatumomab approved in the United States; it was approved in the EU in 2015
First orthogonal Fab interface as solution to LC-association issue[29]
#13
• First demonstration of the bsAb concept[3]
• First fragment-based format[3]
#5
• Hybrid hybridoma (quadroma) pioneered[18]
• First asymmetric format[18]
Invention of the scFv fragment[212]
First solution to LC-association issue through species-restricted LC pairing[30]
#10
Discovery and elucidation of bispecific human IgG4 Fab-arm exchange process in vivo[219]
DVD-Ig symmetric format pioneered[27]
#23
First symmetric format[217]
#21
Generation of bispecific IgG1 through Fab-arm exchange of separately expressed antibodies[51,52]
#12
Domain crossover as solution to LC-association issue[32]
#15
Emicizumab approved in the United States; it was approved in the EU in 2018

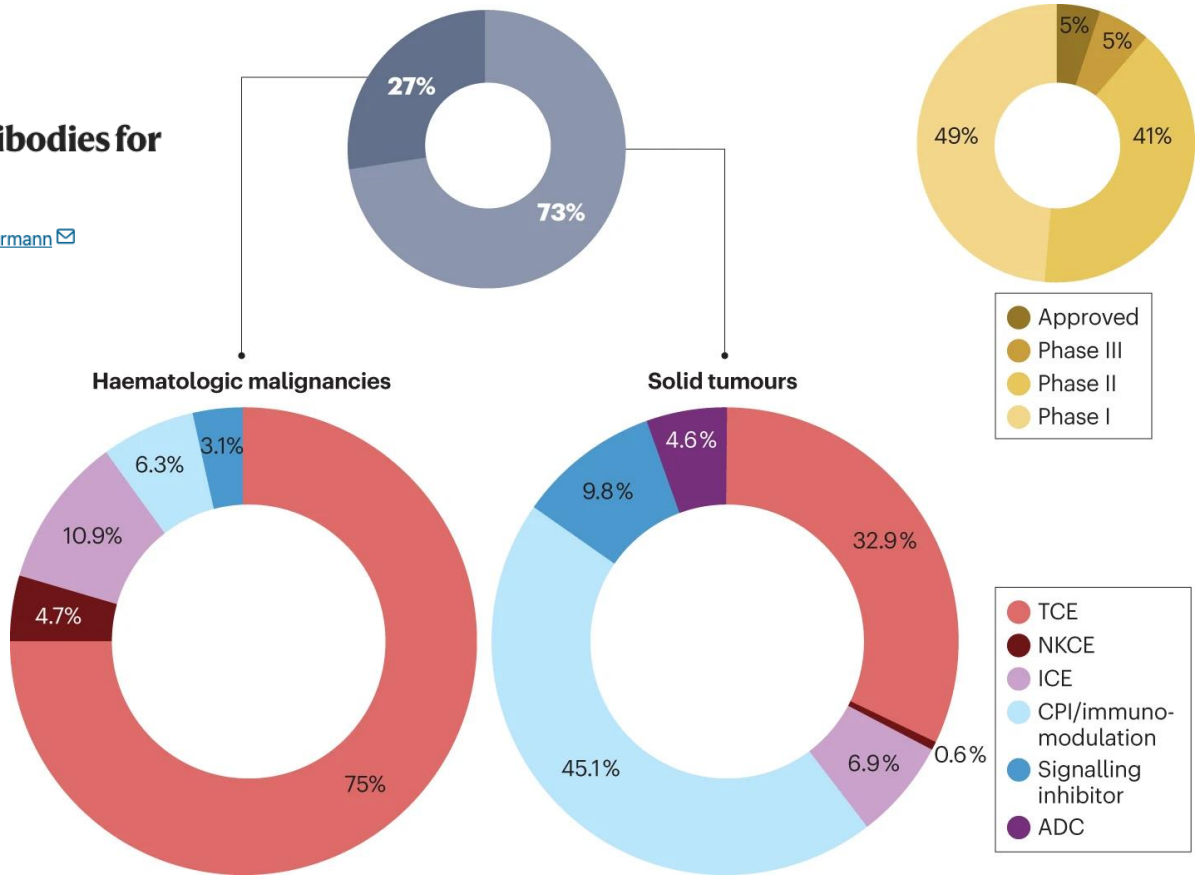
nature reviews drug discovery

Review Article | Published: 06 March 2024

The present and future of bispecific antibodies for cancer therapy

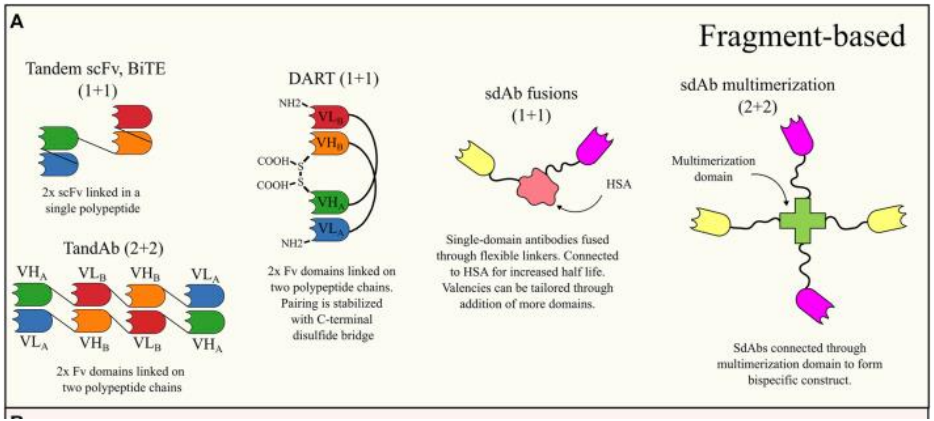
Christian Klein, Ulrich Brinkmann, Janice M. Reichert & Roland E. Kontermann

Nature Reviews Drug Discovery **23**, 301–319 (2024) | Cite this article



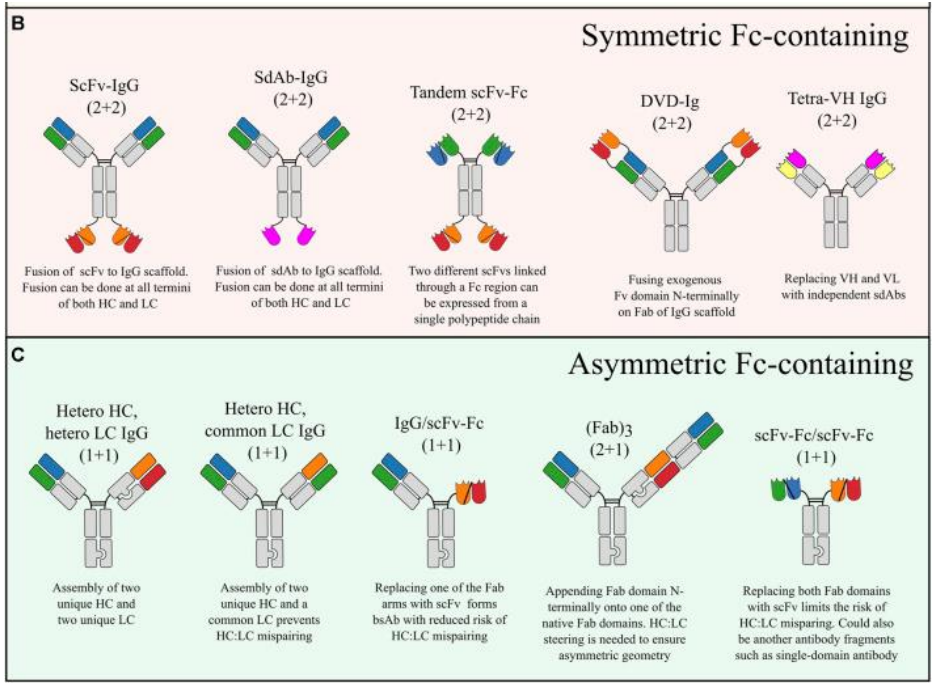
BsAbs structure and classification

Fragment-based bsAbs are composed of the **variable light and heavy domains from two antibodies**, or the Fab units, and lack the Fc region which distinguishes them from IgG-Based bsAbs. These fragments are bound together by **linkers**.



Madsen AV, Front Bioeng Biotechnol. 2024
Sun Y, Acta Pharm Sin B. 2023

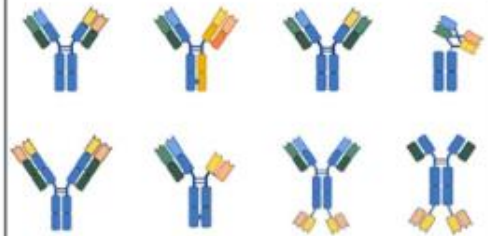
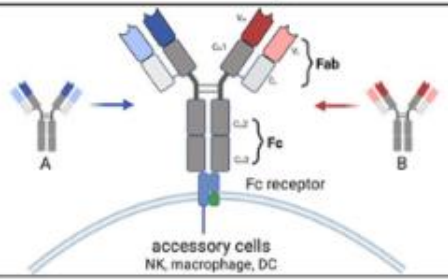
Immunoglobulin (Ig)-like bsAbs include an IgG Fc region. The presence of an Fc region also has consequences for Fc-mediated effector functions such as antibody-dependent cellular cytotoxicity (ADCC), complement fixation (CDC), and the **long half-life resulting from their larger size and FcRn-mediated recycling processes**



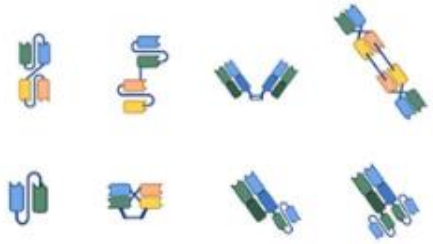
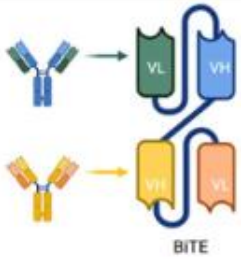
Simone Ragaini, MD

BsAbs structure and classification

IgG-like BsAbs (with Fc regions)

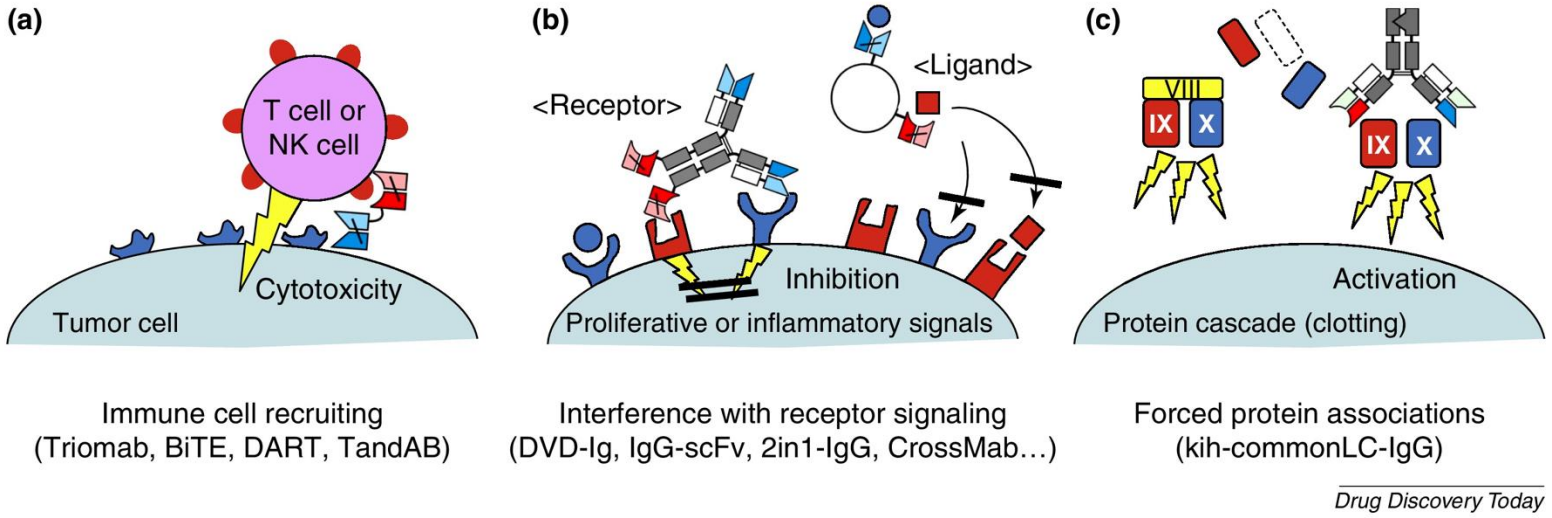
schematic drawing	classical design	characterictics
		long half-life high solubility increased stability CDC ADCC ADCP

Non-IgG-like BsAbs (without the Fc region)

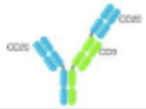
schematic drawing	classical design	characterictics
		short half-life better tissue penetration lower immunogenicity reduced non-specific activation of the innate immune system

Shui et al. Molecular Cancer 2025

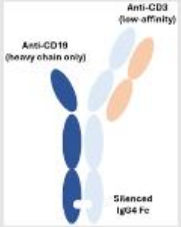
BsAbs functional classification



Kontermann RE, Drug Discov Today. 2015

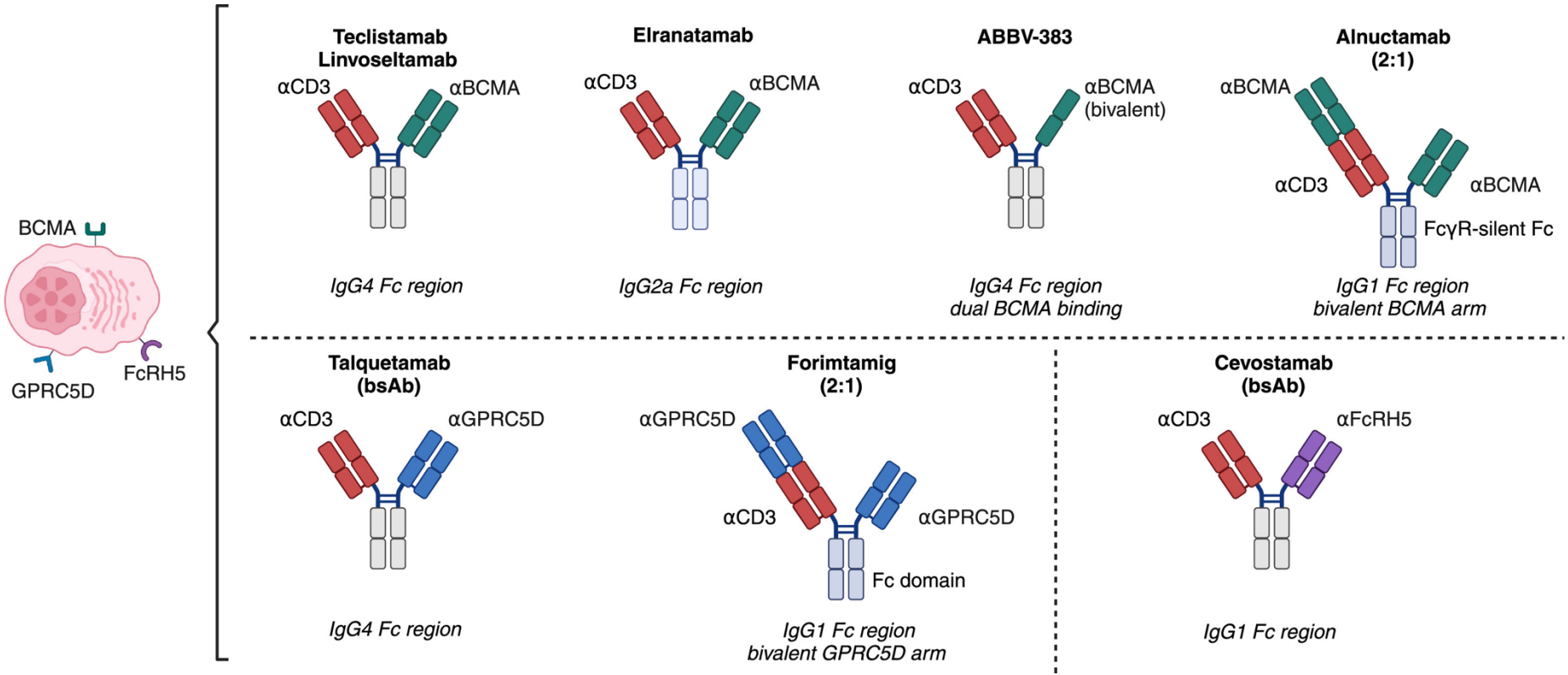
Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio	CD3 clone	CD20 clone	Fc silencing mutations*
Mosunetuzumab[18]		IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9 (CD3δε)	2H7 (type 1 epitope, identical to rituximab)	N297G (no FcγR binding)
Glofitamab[15]		IgG1	Head-to-tail fusion	2:1	SP34-der.(CD3ε)	By-L1 (type 2 epitope, identical to obinutuzumab)	IgG1-P329G-LALA (no FcγR binding)
Epcoritamab[16]		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34-der.)(CD3ε)	7D8 (type 1 epitope, shared by ofatumomab)	L234F,L235E,D265A (no FcγR,C1q binding)
Odronexamab[17]		IgG4	Heavy chains with different affinity	1:1	REG1250 (CD3δε)	3B9-10 (type 1 epitope, shared by ofatumomab)	Modified IgG4 (no FcγRIII binding)

Falchi L, Blood 2023

Surovatamig (AZD0486)	CD19xCD3		IgG4	Knobs-into-holes Low-affinity CD3-binding arm

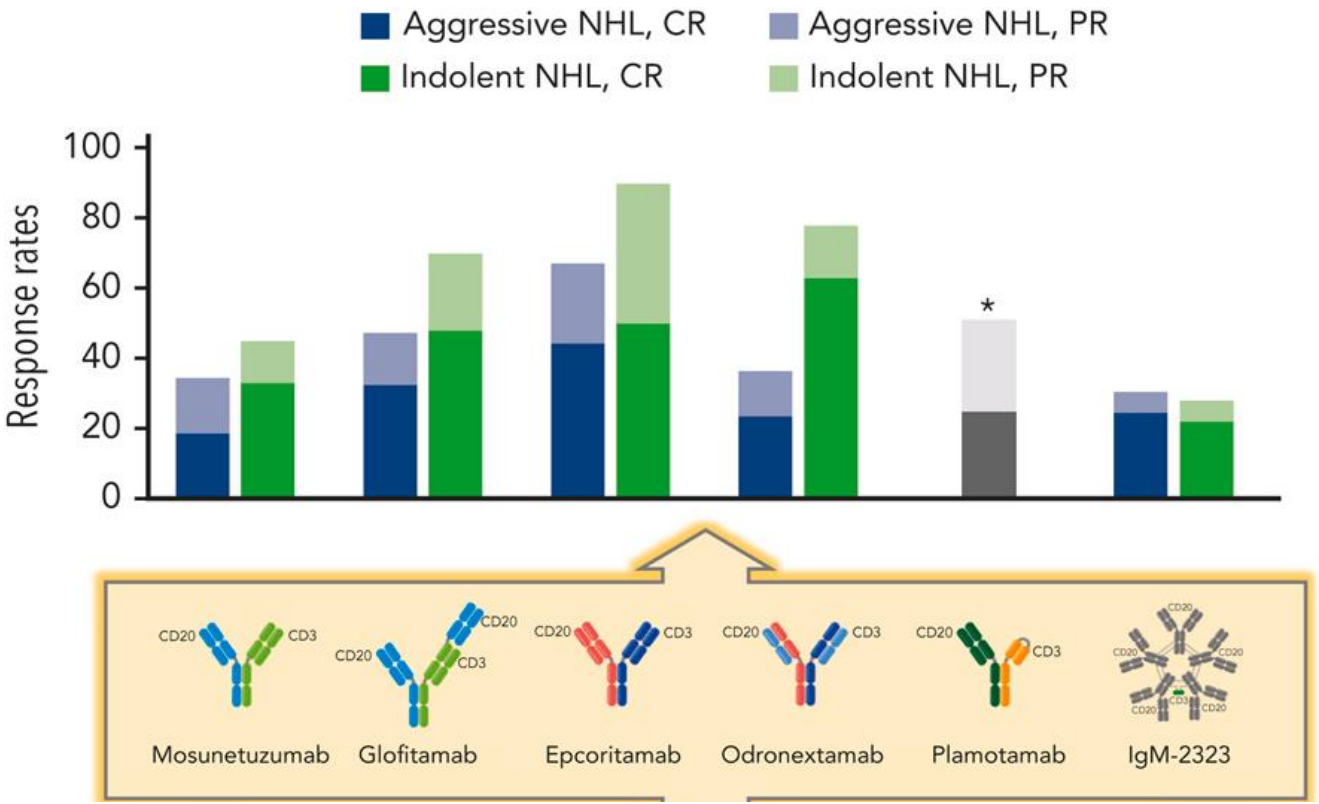
Dong Hyun Kim, Seminars in Hematology 2025

BsAbs in MM



Waldschmidt J, Myeloma and Leukemia, 2024

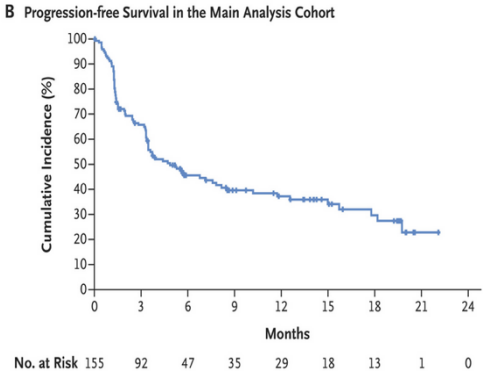
BsAbs in NHLs



Falchi L, Blood 2023

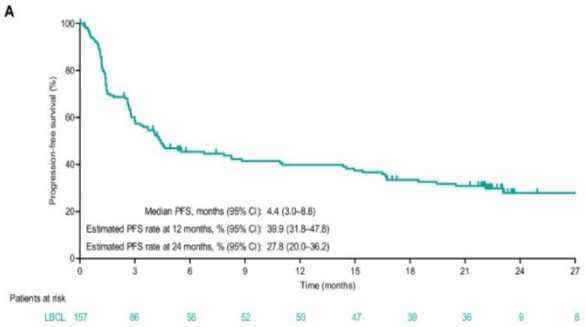
BsAbs in DLBCL

Glofitamab in 3L+ R\R DLBCL



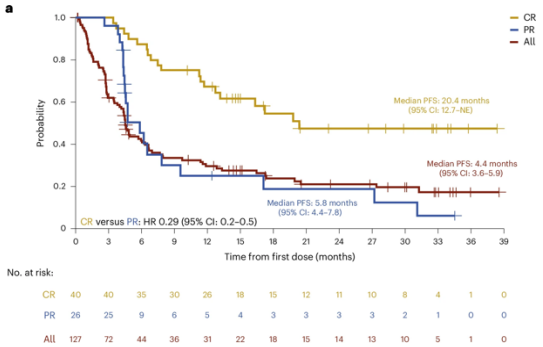
Dickinson M.J, NEJM 2022

Epcoritamab in 2L+ R\R DLBCL



Thieblemont, C Leukemia 2026

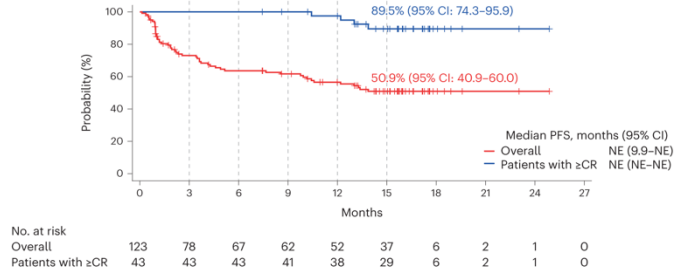
Odronextamab 2L+ R\R DLBCL



Kim, W.S., Nat Cancer 2025

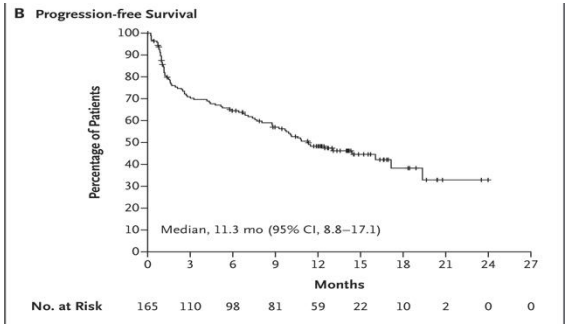
BsAbs in MM

Elranatamab in R\R Triple-exposed MM



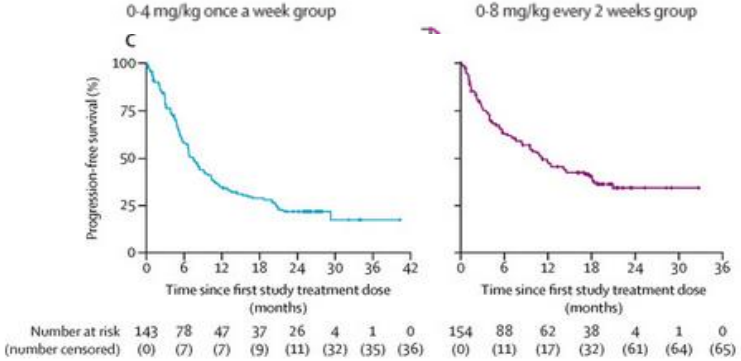
Lesokhin, A.M., Nat Med 2023

Teclistamab in R\R Triple-exposed MM



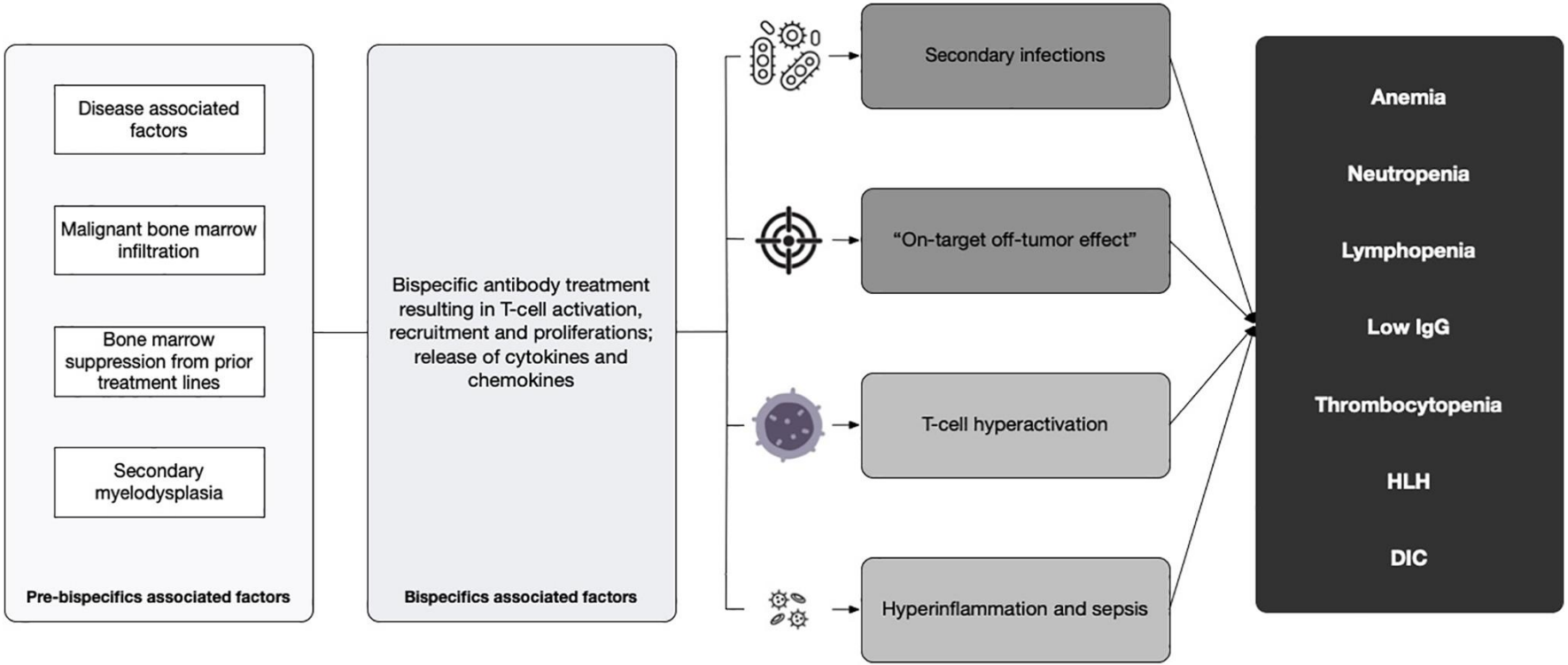
Moreau P et al., NEJM 2022

Talquetamab in R\R Triple-exposed MM



Chari A, Lancet Haematol 2025

Hematological toxicities and Bispecifics

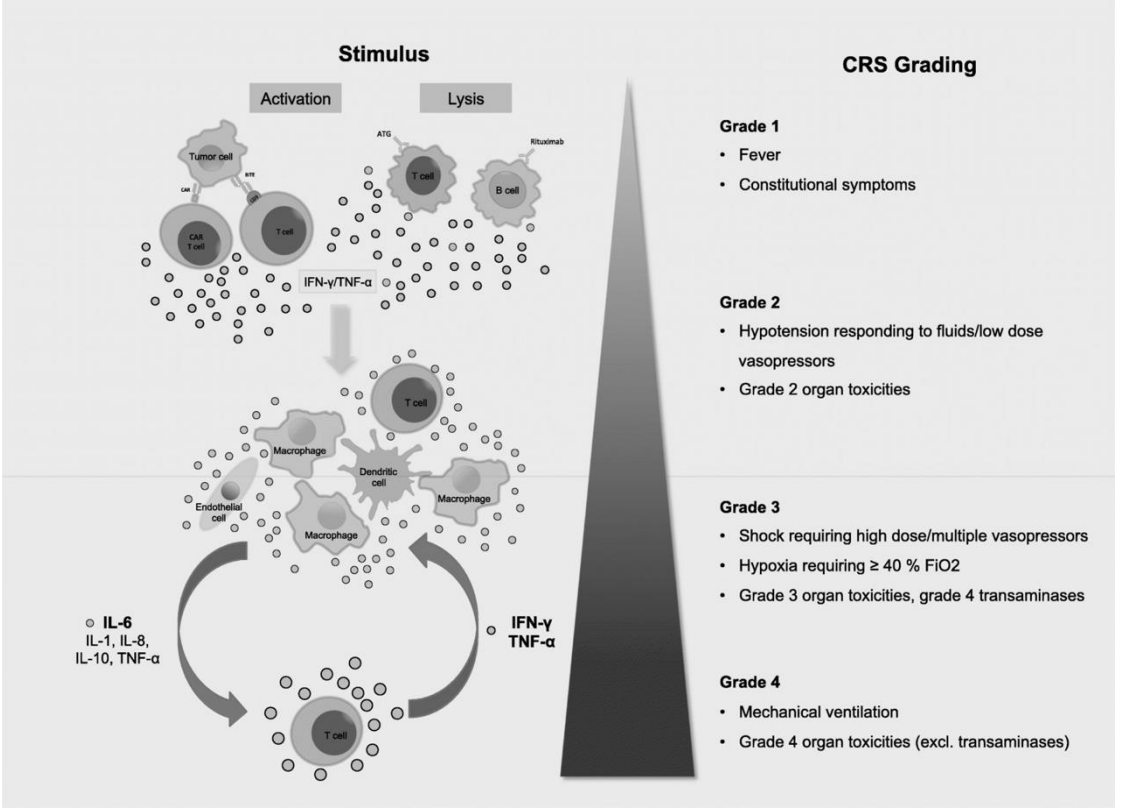


Main cytopenias described after bispecifics administration

Luiz Henrique de Assis, et al. Hematology Am Soc Hematol Educ Program 2023

BsAbs and CRS

- Activation of manly T cells or lysis of immune cells induces a release of IFN-γ or TNF-α.
- This leads to the activation of macrophages, dendritic cells, other immune cells and endothelial cells.
- These cells further release proinflammatory cytokines.
- Importantly, macrophages and endothelial cells produce large amounts of interleukin 6 (IL-6) which in a positive feedback loop manner activates T cells and other immune cells leading to a cytokine storm.



Shimabukuro-Vornhagen A, Journal for ImmunoTherapy of Cancer. 2018

Infections Following Bispecific Antibodies in B-cell Lymphomas

Background:

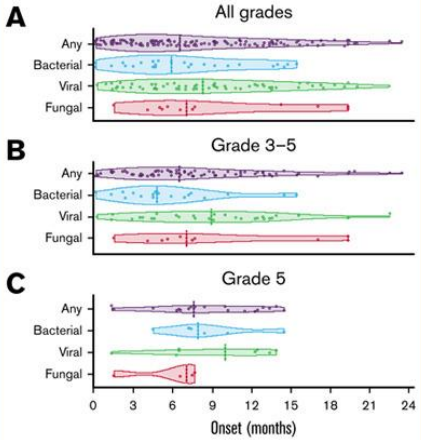
- Bispecific antibodies (BsAb) offer new options for B-cell lymphomas but pose distinct, poorly defined infection risks.

Patients & Methods:

- This is a cohort study of 109 B-cell lymphoma patients who received BsAb therapy between 2016 and 2024.
- The epidemiology, clinical characteristics, and risk factors for BsAb-associated infections were analyzed.

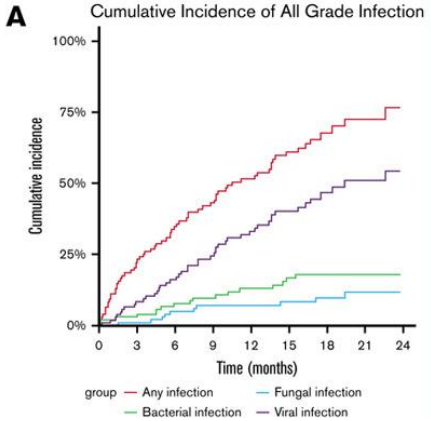
Infection Characteristics:

- Of all infections, 61.2% were grade ≥3.
- The median time to infection was 6.6 months, with bacterial infections occurring earliest.
- Viral infections were most frequent, with SARS-CoV-2 being the leading cause.



Infection Incidence:

- Infections occurred in 62.4%, with 37.6% being grade ≥3.
- Cumulative infection incidence reached 76.4% at 24 months.
- Neutropenia and hypogammaglobulinemia were associated with a higher risk of infection.



Dong Hyun Kim, Blood Adv 2026

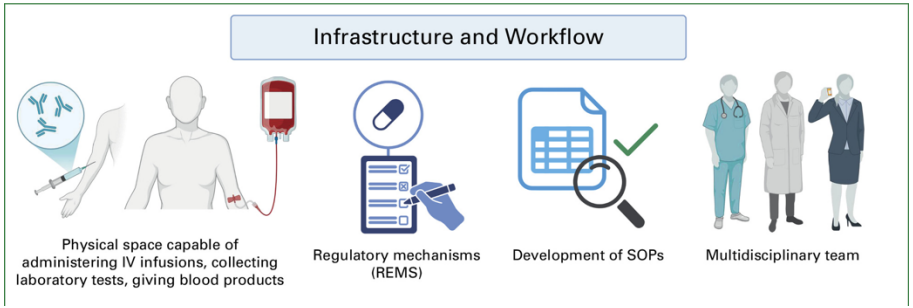
JCO® Oncology Practice
An American Society of Clinical Oncology Journal

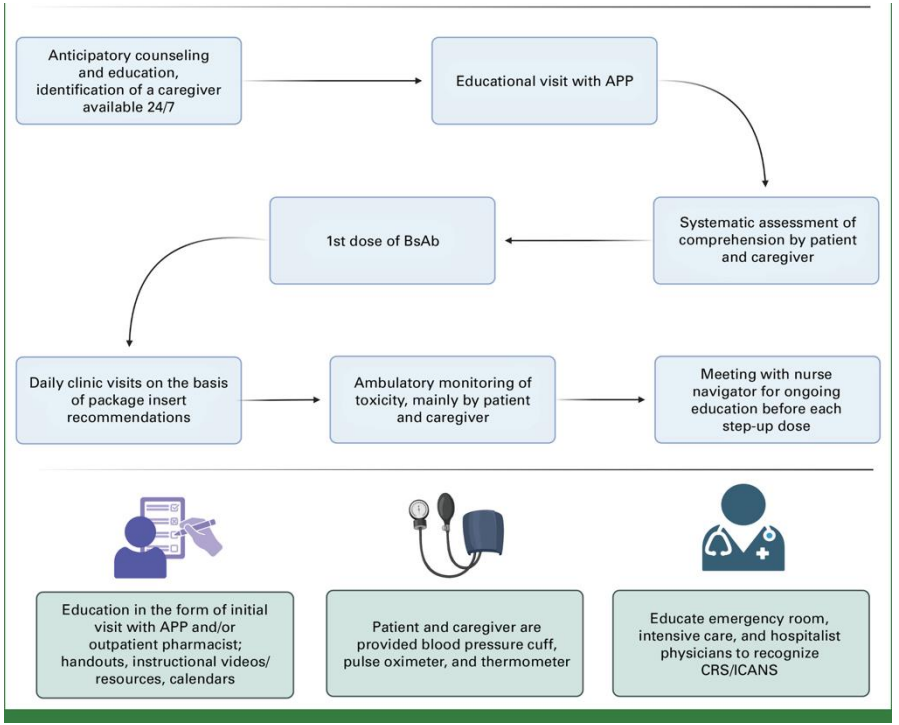
REVIEWS | December 04, 2025 | Latest version

Outpatient Administration of Bispecific Antibody Therapy for Hematologic Malignancies: A Practical Guide

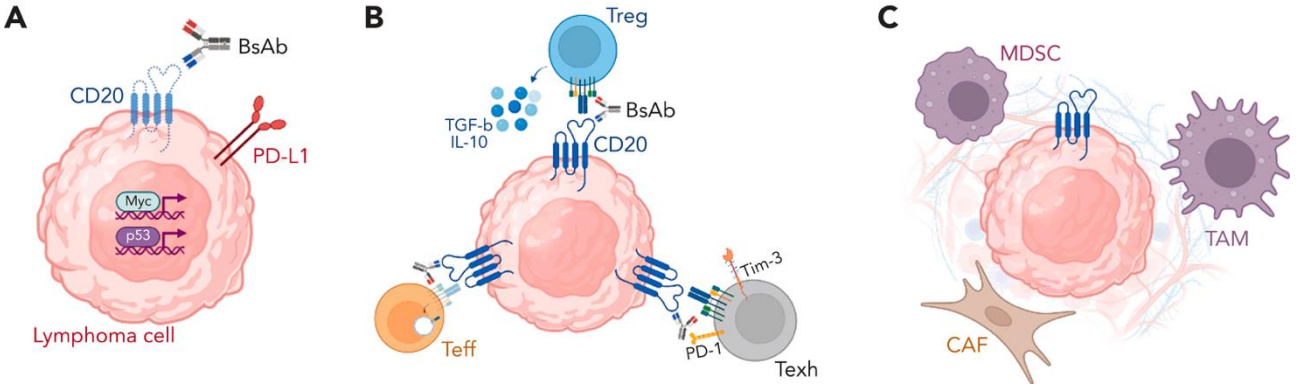
Kian J. Rahbari, MD[1]; Raul del Toro Mijares, MD[2]; Kathryn Kennedy, RN[3]; Leslie Mader, RN[3]; Salyka Sengsayadeth, MD[3]; Reena V. Jayani-Kosarzycki, MD[3]; James Jerkins, MD[3]; Andrew Jallouk, MD[3]; Tae Kon Kim, MD[3]; Shakthi Bhaskar, MD[3]; Vivek G. Patel, MD[2]; Brittney Baer, RN[3]; Sarah Moseley, RN[3]; David Morgan, MD[3]; Bipin N. Savani, MD[3]; Adetola Kassim, MD[3]; Muhamed Baljevic, MD[3]; Olalekan Oluwole, MD[3]; and Bhagirathbhai Dholaria, MBBS, FACP[3]

DOI https://doi.org/10.1200/OP-25-00652





Three Overlapping Pillars of Resistance



Falchi L, Blood 2023

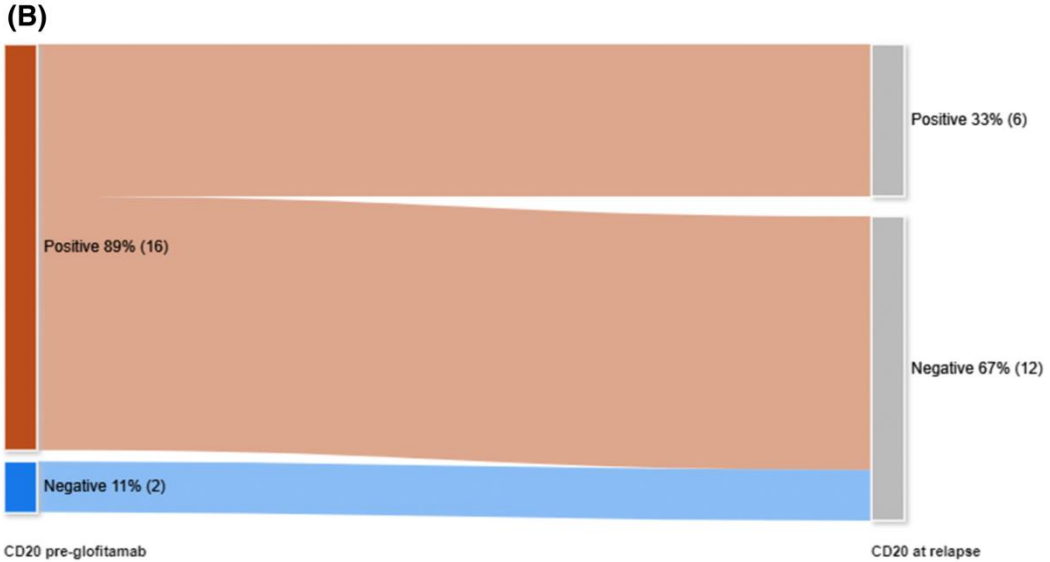
Tumor-Intrinsic Factors	T-Cell Dysfunction	Microenvironmental Barriers
▸ CD20 loss / MS4A1 mutations	▸ Low “fresh” T-cell presence	▸ PD-L1 checkpoint upregulation
▸ NOTCH1 alterations	▸ Lower cytoxic activity	▸ DZ-like spatial exclusion

Maher et al. Cells 2026

Three Overlapping Pillars of Resistance - Tumor-Intrinsic Factors

Selective pressure may drive the activation of programs that promote Antigen-Related Escape

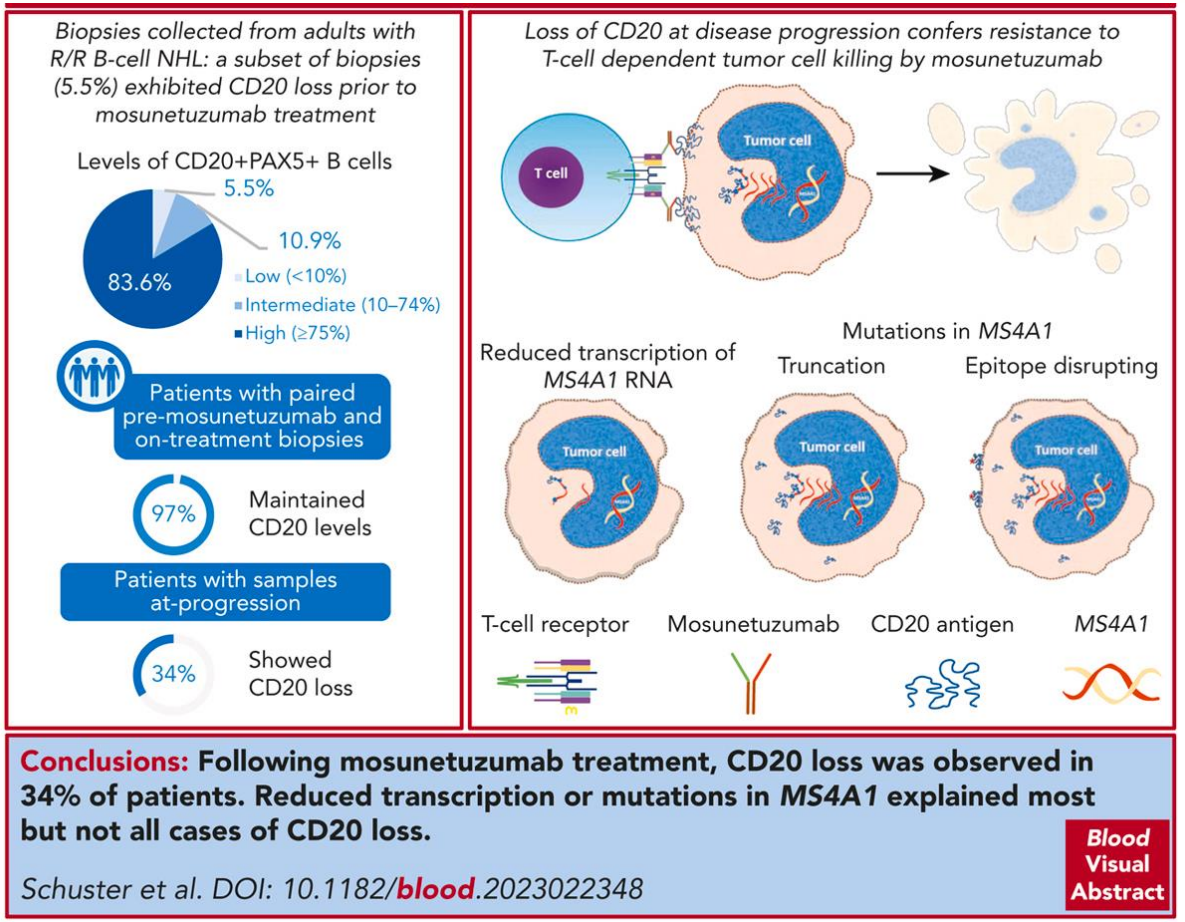
- Cases with aggressive B-NHL R\R after **glofitamab** at the Peter MacCallum Cancer Centre and Royal Melbourne Hospital.
- CD20 status was determined by local pathology review **using IHC with an L26 antibody**
- At progression post-glofitamab, CD20 status was described in 22 patients with available biopsies: **10 had converted from CD20 positive to CD20 negative;** and 2 remained persistently CD20 negative



Grigg S, Br J Haematol. 2024

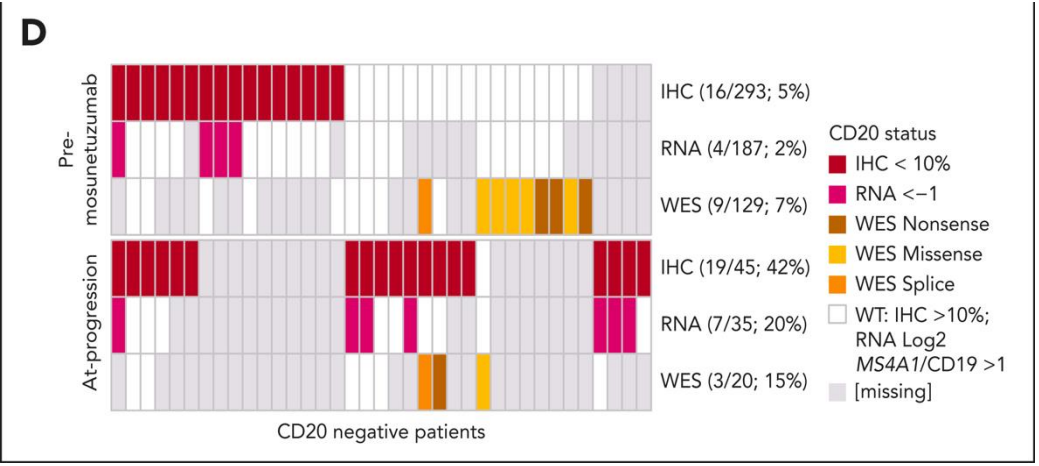
- **CD20 is encoded by *MS4A1***, is a member of the membrane-spanning 4-domain family, subfamily A (MS4A)
- Patient **biopsy specimens were collected** in the phase 1/2 GO29781 trial of **mosunetuzumab monotherapy** for adults with R/R B-cell NHL who had received ≥2 prior therapies.
- IHC (CD20/PAX5) + RNAseq (*MS4A1* expr) + WES (MS4A1 mutation)

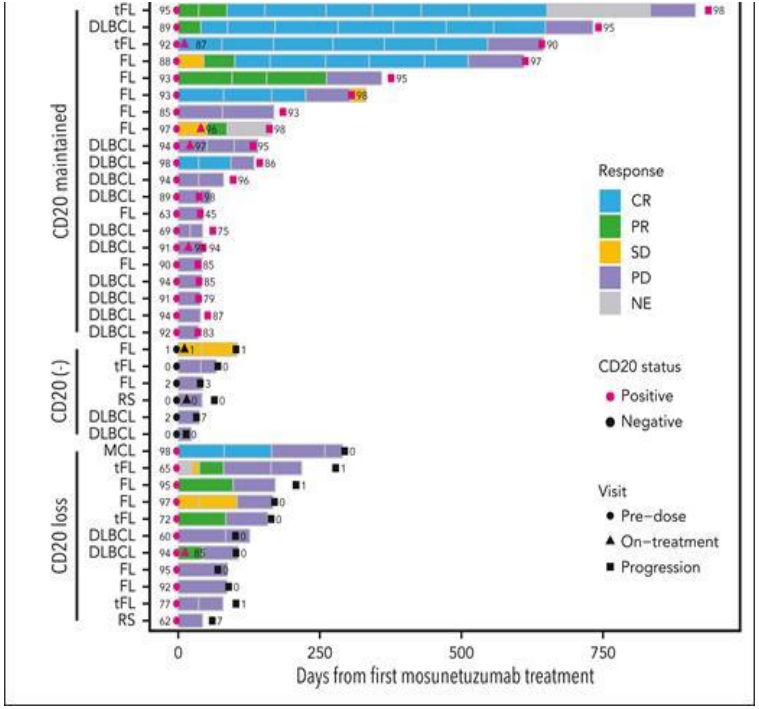
Stephen J. Schuster, Blood 2024



- **CD20 loss at progression** was observed in patients with evidence of **transcriptional downmodulation or with mutations identified by WES.**

- There was also evidence of reduced CD20 levels in the absence of downregulated transcription or exonic mutations in CD20

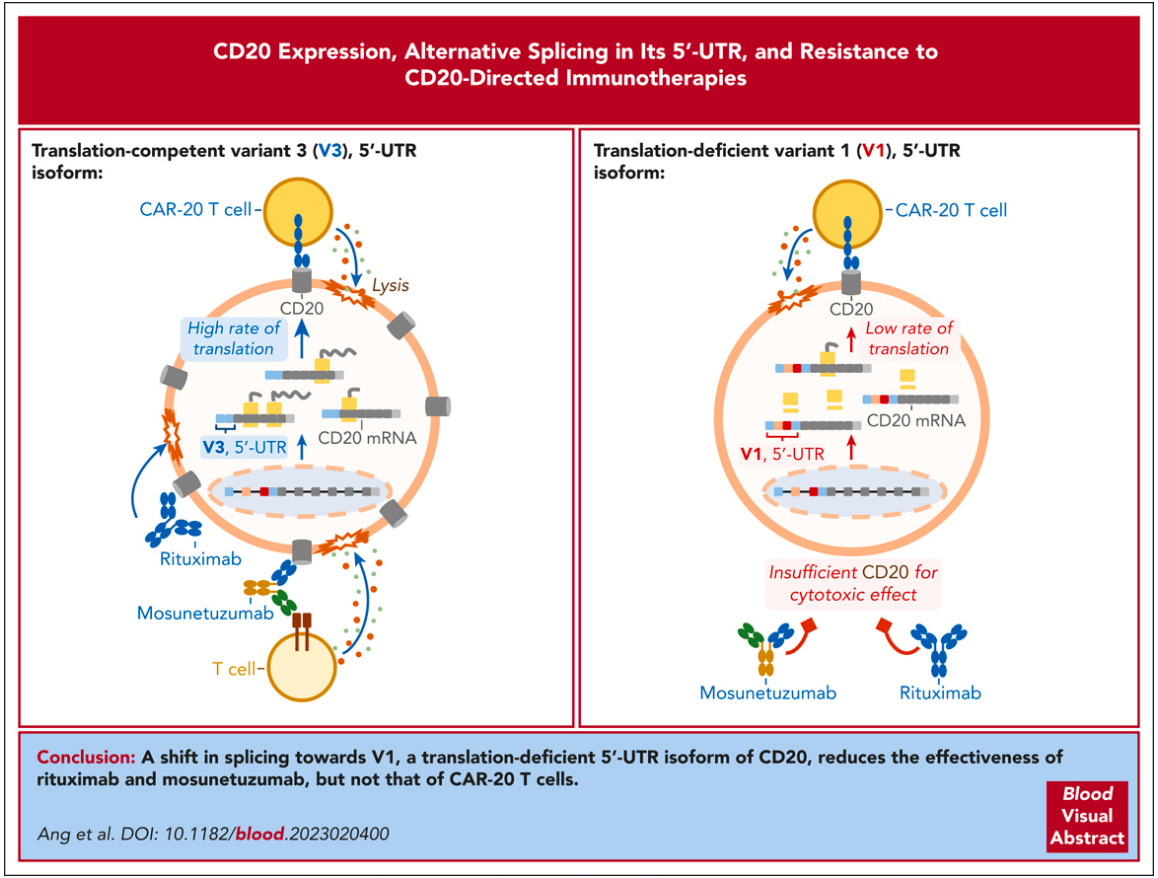




Shorter PFS can in part be explained by CD20 loss before mosunetuzumab or at progression, however, **a subset of patients was refractory and exhibited limited PFS despite maintaining CD20 levels**

Stephen J. Schuster, Blood 2024

Three Overlapping Pillars of Resistance - Tumor-Intrinsic Factors



NOTCH1 Mutations Are Associated With Therapy-Resistance in Patients With B-Cell Lymphoma Treated With CD20xCD3 Bispecific Antibodies

Emil R. Kyvsgaard, Morten Grauslund, Lene Sjø, Linea Cecilie Melchior, Trine Lønbo Grantzau, Lise Mette Rahbek Gjerdrum, Trine Trab, Lærke Sloth Andersen, Anne Ortved Gang ... See all authors

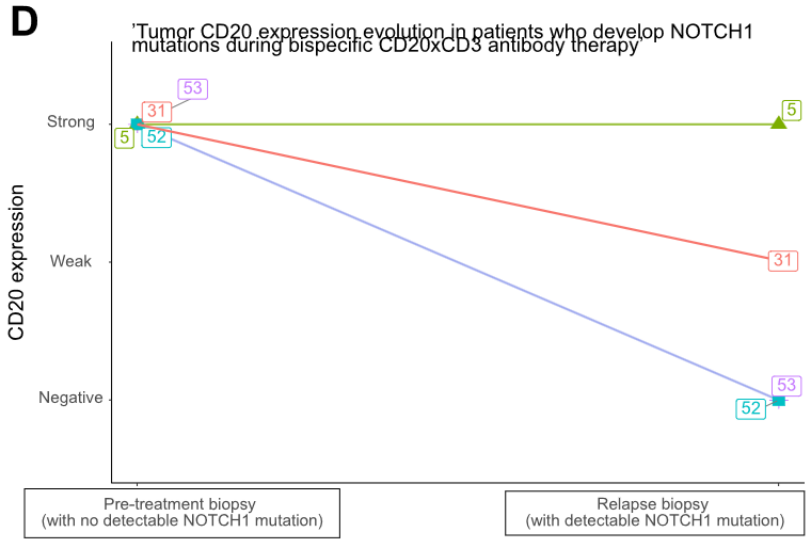
American Journal of Hematology AJH

First published: 25 January 2025 | https://doi.org/10.1002/ajh.27601 | VIEW METRICS

- 56 patients from Rigshospitalet, Copenhagen, and Vejle University Hospital, both in Denmark, who received CD20 × CD3 bispecific antibodies between 2017 and 2023 as part of phase 1 or phase 2 clinical trials.

- Pre bispecs *NOTCH1* mutated tumors conferred significantly worse outcomes in Kaplan–Meier analysis of both PFS and OS ($p = 0.02$ and $p = 0.05$,).

- ***NOTCH1* mutated clones expand under the pressure of CD20 × CD3 bispecific antibody therapy** and may constitute an escape mechanism potentially leading to downstream CD20 antigen loss.



Three Overlapping Pillars of Resistance - T-cell related factors (TME)

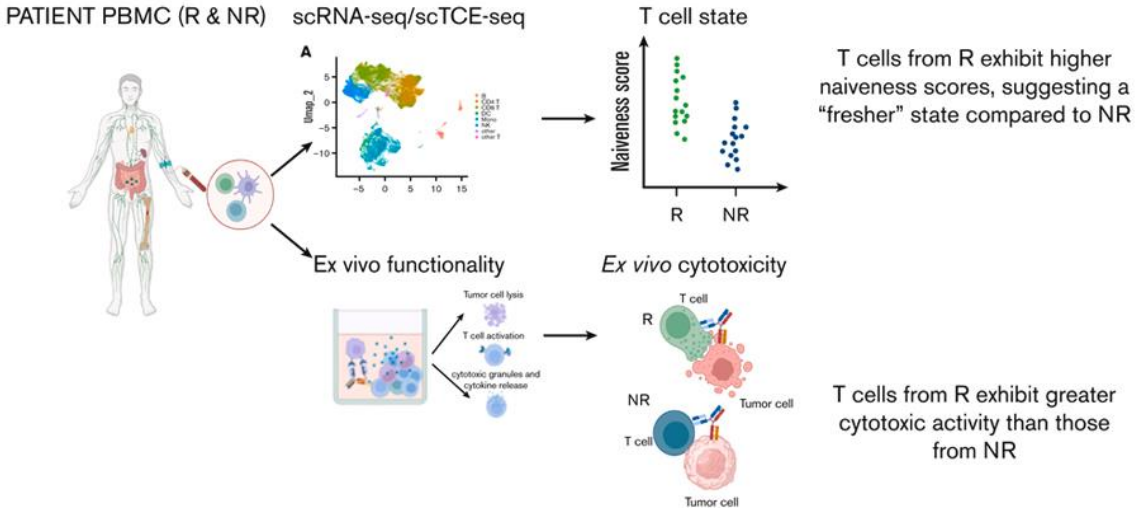
IMMUNOBIOLOGY AND IMMUNOTHERAPY | APRIL 30, 2026

blood advances

Molecular features of response and resistance to glofitamab, a T-cell engager for treatment of large B-cell lymphoma

Stephan Schmeing, Sina Nassiri, Gabrielle Leclercq-Cohen, Emilio Yángüez, Tamara Hüsser, Llucia Alberti Servera, Ramona Schlenker, Johannes Sam, Christian Klein, Pablo Umaña, Sylvia Herter, Alessia Bottos, Marina Bacac

- 30 DBCL pts treated with glofi (18 CMR vs 12 PMD cases)
- PBMCs of these patients collected at baseline and on-treatment time points were subjected to single-cell RNA and TCR sequencing (scRNA-seq/scTCR-seq), flow cytometry, and ex vivo functional assessments



Three Overlapping Pillars of Resistance - T-cell related factors (TME)

IMMUNOBIOLOGY AND IMMUNOTHERAPY | APRIL 30, 2026

blood advances

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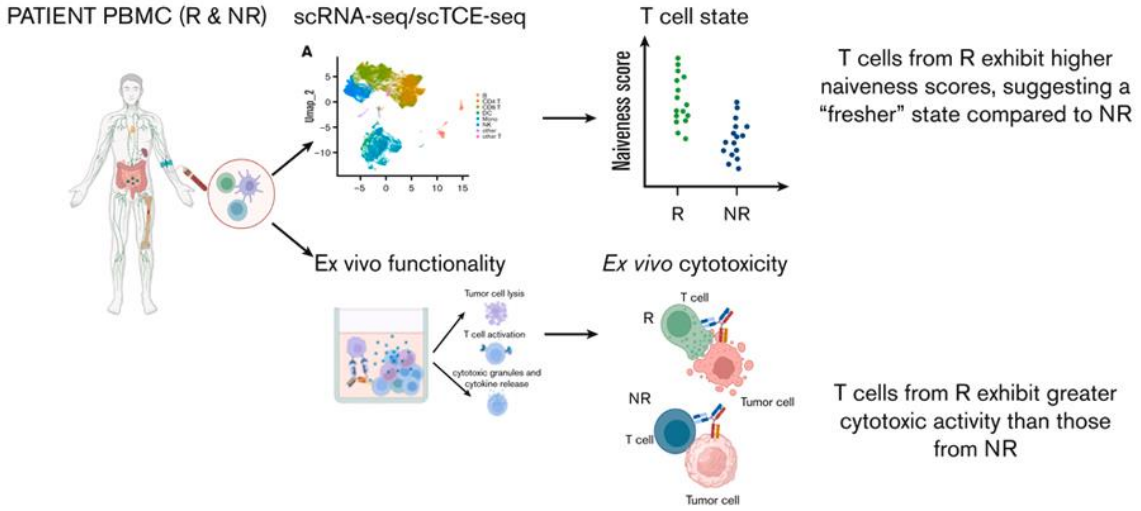
- Maintenance of **naïve-like ("fresher") T-cell states** (particularly the fresher cytotoxic T cells) at **early time points is associated with clinical efficacy.**

- Combination of glofitamab with 4-1BB costimulation translated into increased proportions of intratumor T cells having a fresher, naïve-like phenotype in humanized mouse



Med
Review

Review

T cell exhaustion in bi- and trispecific T cell engager therapy in hematologic malignancies: Mechanisms and implications

Amelie Muth,[1,2,4] Alessandra Holzem,[1,4] Anne-Sophie Neumann,[1,2] Veit L. Buecklein,[1,2] Marion Subklewe,[1,2,3] and Nora Philipp[1,2,*]

Table 2. Pre-existing T cell fitness and exhaustion correlated with TCE therapy response or treatment failure

Pre-therapy T cell fitness/exhaustion				
		Potential biomarkers identified		
TCE	Patient cohort	Responders	Non-responders	Methodology
Epcoritamab	r/r B cell lymphoma	• high $CD4^+$ and $CD8^+$ T cell frequencies (PB and i.t.)	• high $CD8^+TIM\text{-}3^+$, $CD8^+PD\text{-}1^+$, $CD8^+Tim\text{-}3^+TIGIT^+$ (PB)	flow cytometry, IHC
Mosunetuzumab	(r/r) NHL	• high ALC (PB) • $CD8^+$ tumor infiltration	–	flow cytometry, IHC
Blinatumomab	r/r BCP-ALL	• high T_{naive} and T_{CM} cells (PB and BM) • high clonal diversity (PB and BM) • expanded $CD8^+GZMK^+$ T_{EM}-like T cells (PB) • high $CD8^+$ cytotoxicity score (also in MRD^+ BCP-ALL) (PB)	• high T_{reg} frequencies (PB) • enriched exhaustion signature (PB and BM) • high $CD8^+$ dysfunction score (PB)	flow cytometry, scRNA-seq
Teclistamab	r/r MM	• high $CD8^+$ T cell frequencies (PB) • high frequency of $CD8^+GZMB^+$, $CD8^+perforin^+$, $CD4^+GZMB^+$, $CD4^+$ T_{naive}, $CD4^+$ T_{EMRA} (BM) • $CD4^+CD25^+$ T cells correlated with improved PFS (BM) • low $CD3^+PD\text{-}1^+TIM\text{-}3^+$ T cells (PB and BM)	• high $CD38^+$ T_{reg} frequencies (PB) • high $CD8^+PD\text{-}1^+$ (+CD38 or TIM-3) T cells correlated with high disease burden (PB and BM) • similar trend in $CD4^+$ T cells	flow cytometry, CyTOF
Flotetuzumab	r/r AML	• IFN-γ signature • immune-infiltrated TME • 10-gene signature predictive for CR (all BM)	• non-immune-infiltrated TME (BM)	NanoString

ALC, absolute lymphocyte count; AML, acute myeloid leukemia; BCP-ALL, B cell precursor acute lymphoblastic leukemia; BM, bone marrow; CR, complete remission; CyTOF, cytometry by time of flight; IHC, immunohistochemistry; i.t., intratumoral; MM, multiple myeloma; MRD, minimal residual disease; NHL, non-Hodgkin's lymphoma; PB, peripheral blood; PFS, progression-free survival; r/r, relapsed/refractory; scRNA-seq, single-cell RNA sequencing; T_{CM}, central memory T cell; T_{EM}, effector memory T cell; TME, tumor microenvironment; T_{reg}, regulatory T cell.

Amelie Muth,Med, 2026

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blood

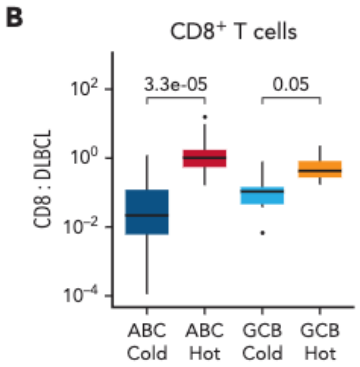
Integrative genomic analysis of DLBCL identifies immune environments associated with bispecific antibody response

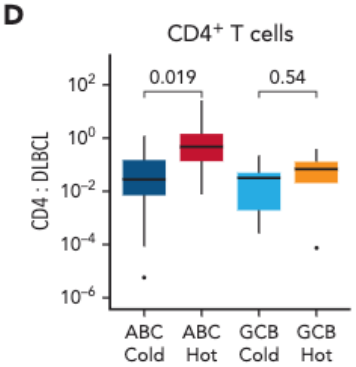
Sravya Tumuluru, James K. Godfrey, Alan Cooper, Jovian Yu, Xiufen Chen, Brendan W. MacNabb, Girish Venkataraman, Yuanyuan Zha, Benedikt Pelzer, Joo Song, Gerben Duns, Brian J. Sworder, Sandeep Raj, Christopher Bolen, Elicia Penuel, Ekaterina Postovalova, Nikita Kotlov, Aleksander Bagaev, Nathan Fowler, Roni Shouval, Sonali M. Smith, Ash A. Alizadeh, Christian Steidl, Justin Kline

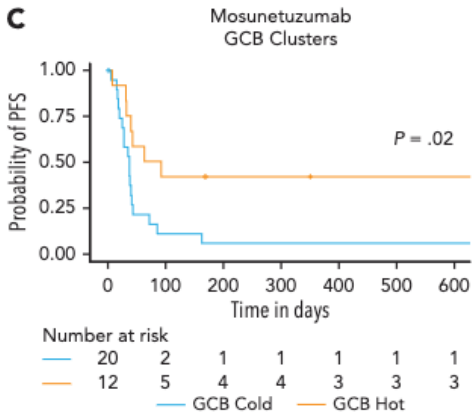
- Bulk transcriptomic analysis on over 500 DLBCL patients, calculating per-sample enrichment scores for 19 gene sets comprising immune-related and COO-related signatures.

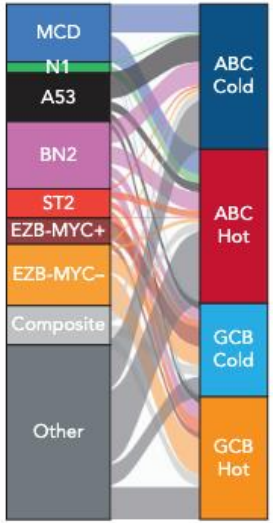
- **DLBCL-immune quadrants (DLBCL-Iqs)** based on COO and immune gene expression signatures: ABC hot; ABC cold; GCB hot; and GCB cold.

- They also noted specific features of the IQs. For instance, "hot" DLBCLs exhibited higher CD8+ T-cell infiltration and activity compared with "cold" DLBCLs.









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T cell exhaustion in bi- and trispecific T cell engager therapy in hematologic malignancies: Mechanisms and implications

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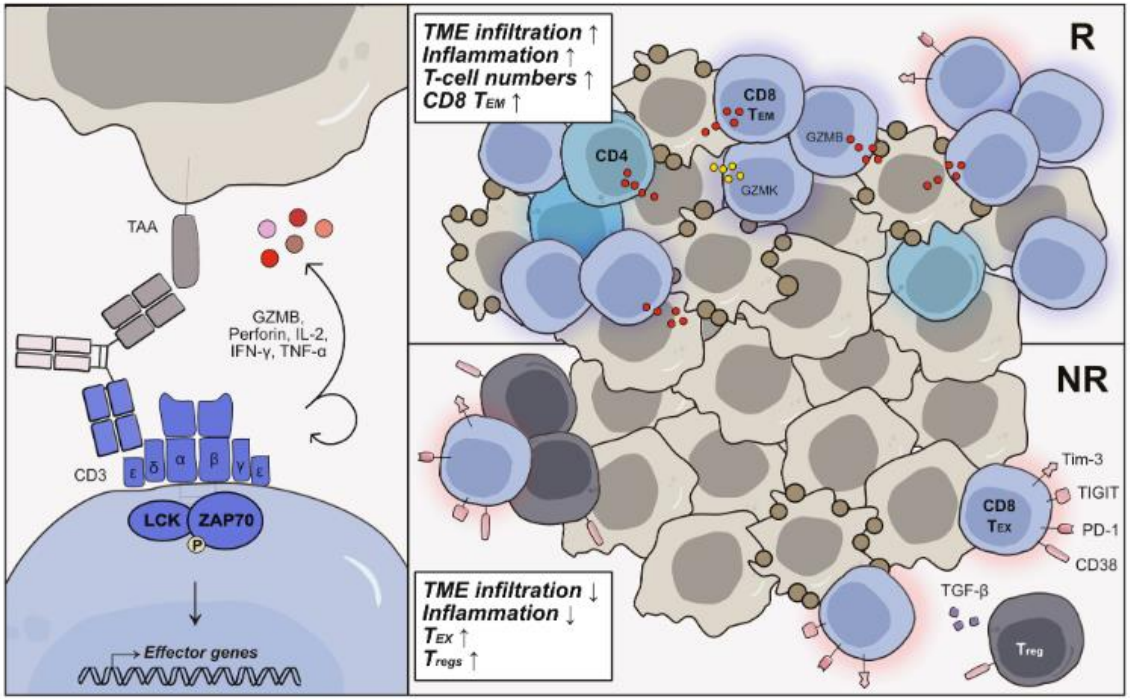


Figure 3. The T cell pool shapes the response to TCE therapy

Left: schematic mechanism of TCE-mediated T cell activation and initiation of effector function. Right: T cell-related biomarkers that predict patient response to TCE therapy. NR, non-responders; R, responders; TAA, tumor-associated antigen; T_{EM}, effector memory T cell; T_{EX}, exhausted T cell; TME, tumor microenvironment; T_{reg}, regulatory T cell.

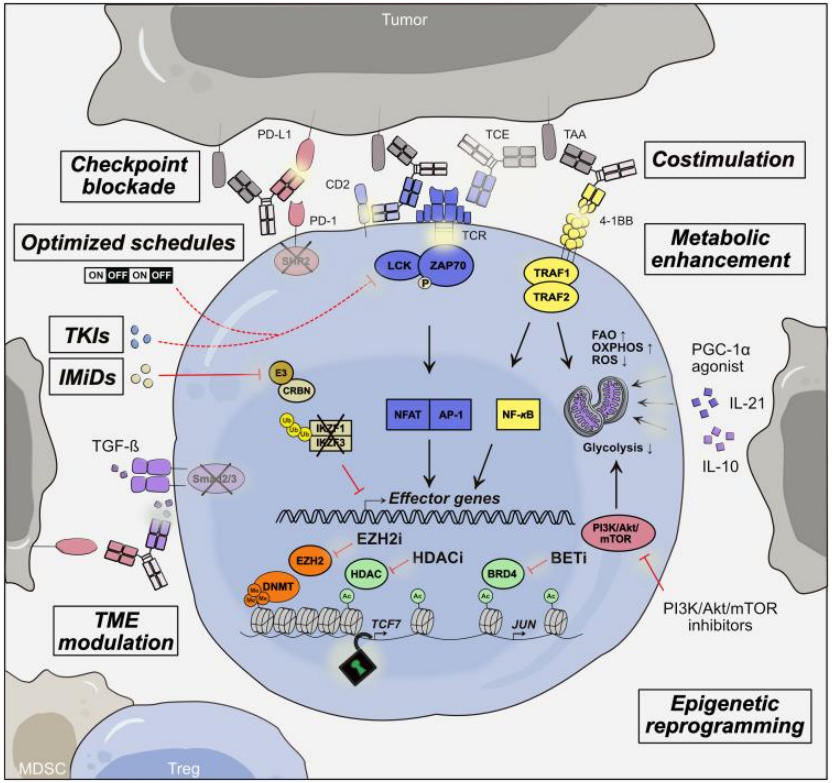
Amelie Muth,Med, 2026

Overcoming Resistance and Future Perspectives

Table 4. Strategies for mitigating T cell exhaustion in TCE therapy

	Patient population	TCE combination (study phase[a])
Strategies in advanced clinical trials (≥ phase 2)		
Tyrosine kinase inhibitors (TKIs)	Ph$^+$ cancers	blinatumomab + ponatinib (phase 2), blinatumomab + dasatinib (phase 2)
Epigenetic modulators	untreated FL	mosunetuzumab + tazemetostat (EZH2 inhibitor) (phase 2)
Strategies in early clinical trials (< phase 2)		
Immune checkpoint blockade (ICB)	r/r ALL, lymphoma	blinatumomab + pembrolizumab (phase 1/2), CD3xCD20 (REGN1979) + anti-PD-1 (REGN2810)
Additional costimulation	r/r B-NHLr/r MM	glofitamab + CD19x4-1BBL (phase 1/2) linvoseltamab + CD38xCD28 (phase 1/2)
Cereblon-modulating agents (CELMoDs)	B cell malignancies	mosunetuzumab + lenalidomide (phase 1) talquetamab + pomalidomide (phase 1)
	Preclinical model	TCE combination
Strategies at the preclinical stage		
Optimized administration schedules	B-ALL, lymphoma	blinatumomab + treatment-free intervals
Metabolic reprogramming	lymphoma	CD3xCD19 TCE + mTOR inhibitor
Modulation of the cellular TME		
Antibody-drug conjugates	MM	CD3xBCMA TCE + daratumumab
Local costimulation	AML	WT1-TCE + FAPx4-1BBL
Secreting T cell-engaging antibody (STAb) T cells	AML, B-ALL, MM	e.g., CD3xCD33 TCE, CD3xCD19 + PD-L1x4-1BB TCE, CD3xCD19 + CD3xBCMA TCE
Modulation of soluble mediators in the TME		
Cytokines	B-ALL, MM	blinatumomab + IL-12; CD3¯CD19-IL-12 "BiTEokine"; CD3xBCMA TCE + IL-21
STING agonism	AML	CD3xCD33 TCE + STING agonist

AML, acute myeloid leukemia; B-ALL, B acute lymphoblastic leukemia; FL, follicular lymphoma; MM, multiple myeloma; Ph$^+$, Philadelphia chromosome positive; TCE, T cell engager; TME, tumor microenvironment.
[a]Only the most advanced studies are indicated.

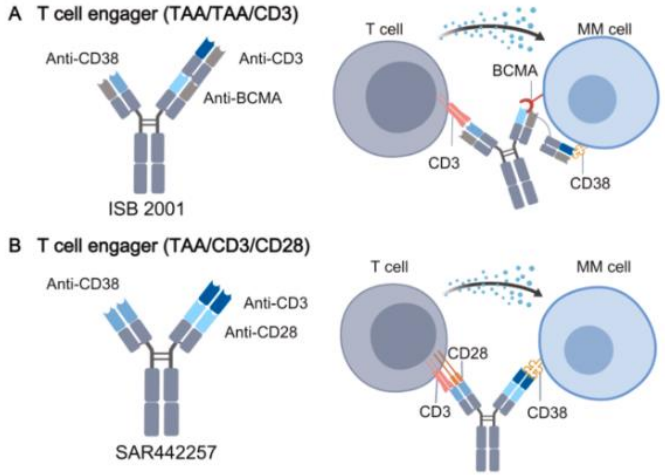


Amelie Muth,Med, 2026

Overcoming Resistance and Future Perspectives – Good things come in threes

- **Dual Tumor Antigen Targeting Strategy**: By requiring concurrent engagement of 2 distinct tumor antigens for full T cell activation, trispecific molecules establish a higher activation threshold and reduce the probability of immune escape through single antigen loss.

- **Co-Stimulatory Integration Strategy:** By incorporating binding domains for co-stimulatory receptors such as CD28 or 4-1BB, these constructs provide both signal 1 (antigen recognition through CD3) and signal 2 (co-stimulation) in a single molecule, potentially overcoming T cell exhaustion in heavily pretreated patients



Koh KN, Semin Hematol. 2025
Liu X, Int Immunopharmacol. 2026

Take-home messages and conclusions

Practice-changing class
BsAbs are now standard of care in R/R NHL and MM

Accessible immunotherapy
Off-the-shelf; no manufacturing delay vs CAR-T

Manageable but real toxicity
CRS, infections, cytopenias require structured monitoring

Resistance is multifactorial
CD20 loss, T-cell exhaustion, immunosuppressive TME

Biomarkers needed
Immune contexture (hot/cold), ctDNA/MRD to guide therapy

Expanding role ahead
Earlier lines, combinations, trispecifics in development

Understanding and overcoming resistance
is the central challenge — requiring integrated multi-omic approaches

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THANK YOU

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