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CAR-T Cells and Bispecific Antibodies in R/R DLBCL: From Competition to Integration

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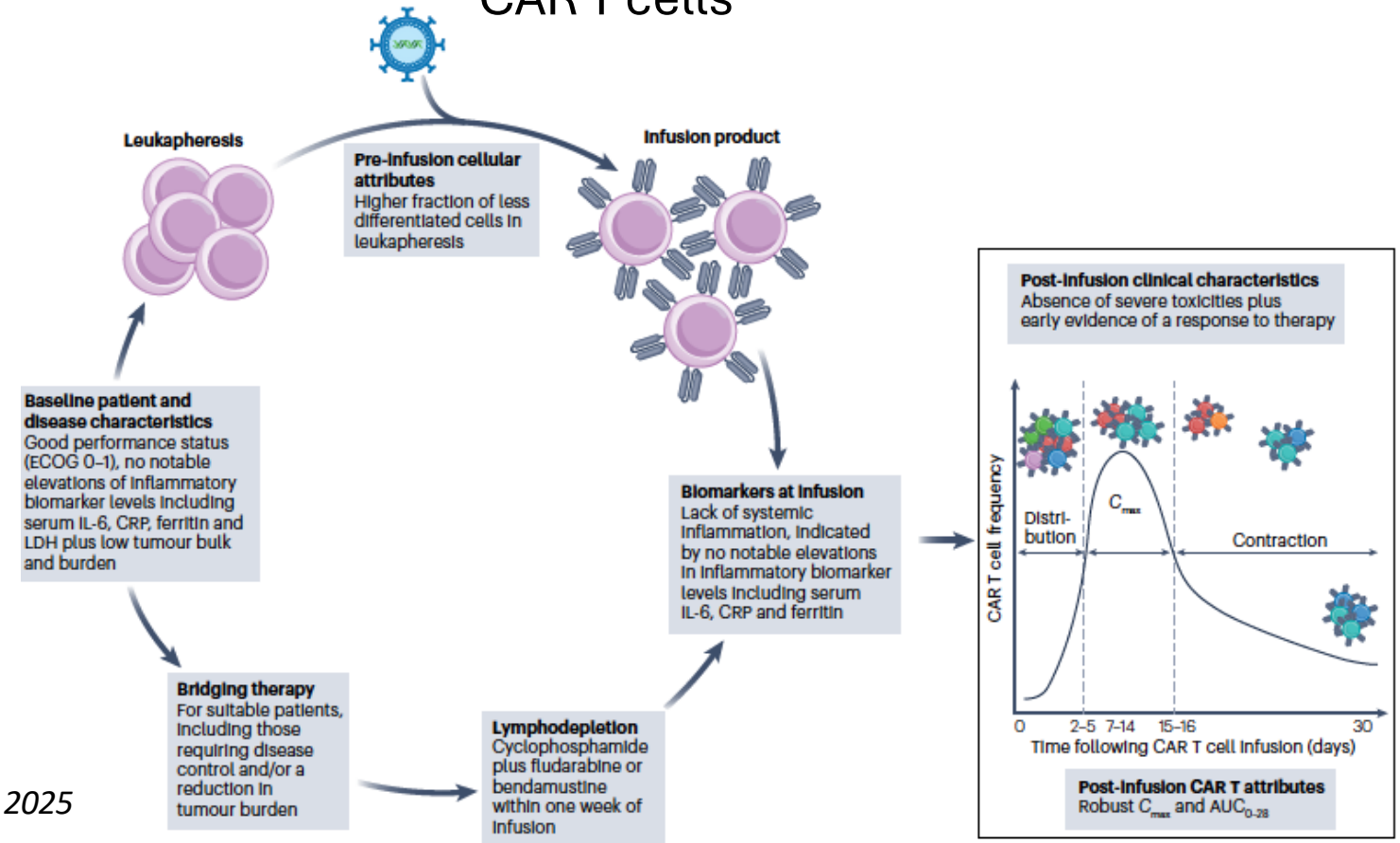
Disclosures of Carmelo Carlo-Stella

Company name	Research support	Consultant	Stockholder	Advisory board	Other
ADC Therapeutics	X	X		X	Honorarium
Karyopharm Tx				X	Honorarium
Celgene/BMS				X	Honorarium
Incyte				X	Honorarium
Hoffmann-La Roche Ltd	X			X	Honorarium
Janssen Oncology				X	Honorarium
Takeda				X	Honorarium
Merck Sharp & Dohme				X	Honorarium
AstraZeneca				X	Honorarium
Gilead				X	Honorarium
SOBI				X	Honorarium
AbbVie				X	Honorarium
Genmab				X	Honorarium

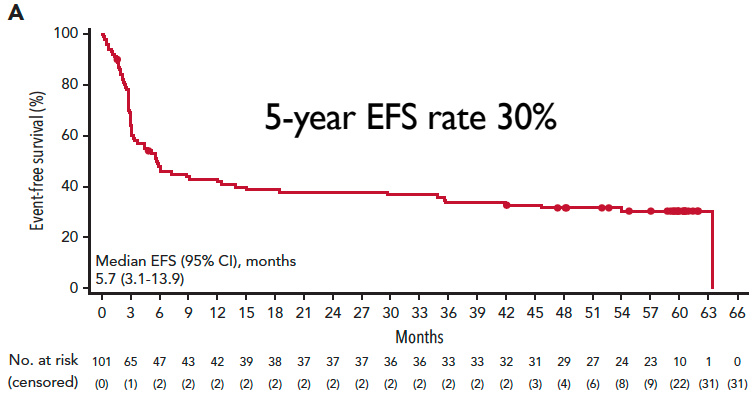
Factors associated with improved efficacy of CD19-targeted CAR T cells

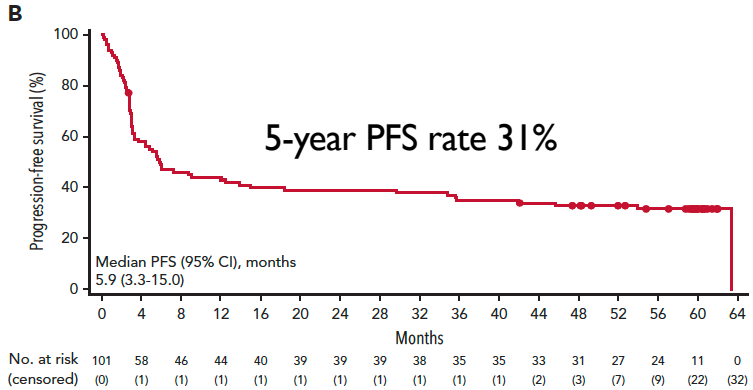


Bock T., Nat Med 2025

ZUMA 1 (3L+) after 5 years of follow-up

	N = 101
Best response, n (%, 95% CI)	
Objective response	84 (83, 74-90)
CR	59 (58, 48-68)
PR	25 (25, 17-34)



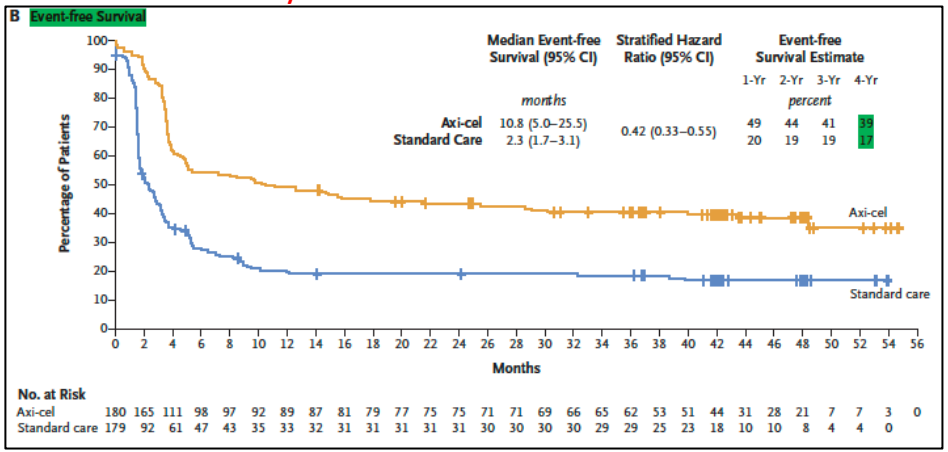


ZUMA-1. Neelapu S et al, Blood 2023

Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma

J.R. Westin, O.O. Oluwole, M.J. Kersten, D.B. Miklos, M.-A. Perales, A. Ghobadi, A.P. Rapoport, A. Sureda, C.A. Jacobson, U. Farooq, T. van Meerten, M. Ulrickson, M. Elsawy, L.A. Leslie, S. Chaganti, M. Dickinson, K. Dorritie, P.M. Reagan, J. McGuirk, K.W. Song, P.A. Riedell, M.C. Minnema, Y. Yang, S. Vardhanabhuti, S. Filosto, P. Cheng, S.A. Shahani, M. Schupp, C. To, and F.L. Locke, for the ZUMA-7 Investigators and Kite Members*

5-year EFS rate 39% vs 17%

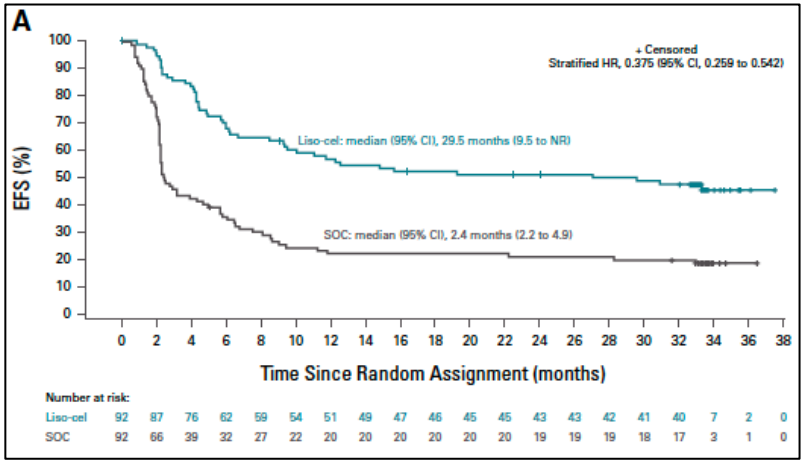


ZUMA-7 – Westin J et al, NEJM, 2023

Lisocabtagene Maraleucel Versus Standard of Care for Second-Line Relapsed/Refractory Large B-Cell Lymphoma: 3-Year Follow-Up From the Randomized, Phase III TRANSFORM Study

Manali Kamdar, MD, MBBS[1]; Scott R. Solomon, MD[2]; Jon Arnason, MD[3]; Patrick B. Johnston, MD, PhD[4]; Bertram Glass, MD[5]; Veronika Bachanova, MD, PhD[6]; Sami Ibrahimi, MD[7]; Stephan Mielke, MD[8]; Pim Mutsaers, MD[9]; Francisco Hernandez-Ilizaliturri, MD[10]; Koji Izutsu, MD, PhD[11]; Franck Morschhauser, MD, PhD[12]; Matthew Lunning, DO[13]; Victor A. Chow, MD[14]; Sandrine Montheard, MS[15]; Josu Santamaria, MSc[15]; Silvia Colicino, PhD[15]; Ken Ogasawara, PhD, MPH[16]; Lara Stepan, BS[14]; Fei Fei Liu, GDCE, MBA[16]; and Jeremy S. Abramson, MD, MMSc[17]

3-year EFS rate 46% vs 19%



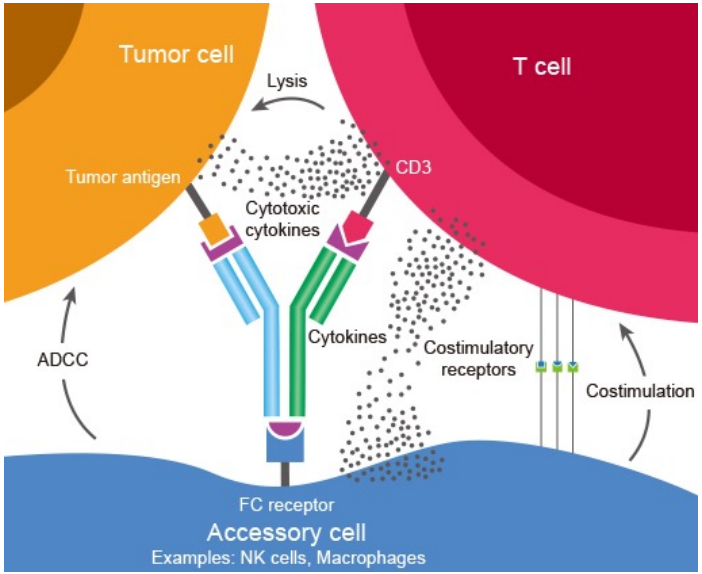
Kamdar M., JCO 2025

CAR-T Cell Therapy has a Curative Potential but … we are Still Facing a High Relapse Rate

- Approximately 50% of CAR-T cell recipients relapse

- Manufacturing-related selection bias

Immune Synapse

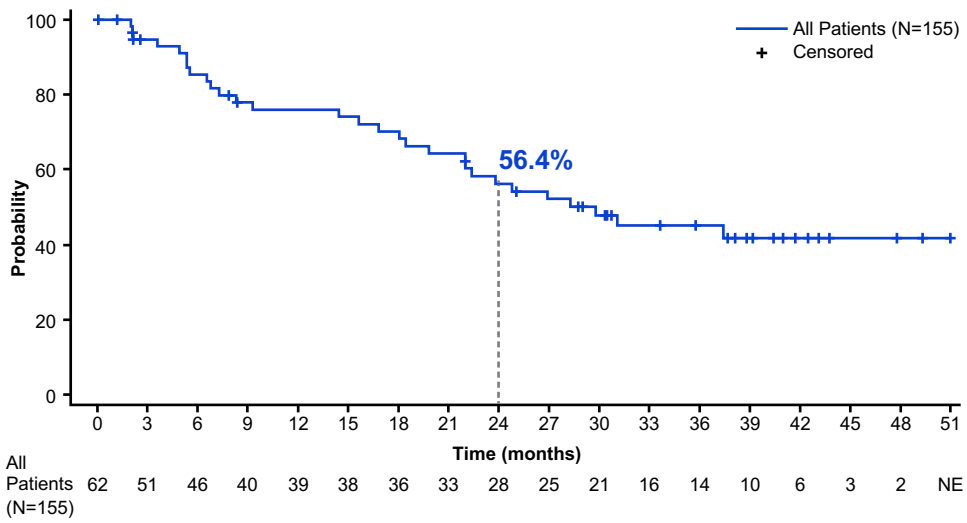


- *Simultaneous binding* to CD20 on tumor cells and CD3ε chain of the TCR on T cells results in the formation of **an immune synapse**
- T cell activation and release of perforins and granzymes result in **T cell-dependent killing of the tumor cell**.
- Both CD4+ and CD8+ T-cell subsets can eliminate tumor cells, but the onset of CD4+ T cell-mediated killing is delayed compared with CD8+ T cell-mediated killing
- T cell-mediated tumor cell killing **without the need for antigen recognition** by MHC class I or II molecules, antigen-presenting cells, or costimulatory molecules

CR remained durable following fixed duration glofitamab treatment: 3-year follow-up from a pivotal Phase II study

	(N=155)*
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]
Median DoCR,† months (95% CI)	29.8 (22.0–NE)
24-month DoCR, % (95% CI)	56.4 (42.9–69.8)
Ongoing CRs, n/N (%)	33/62 (53.2)
Median CR follow-up, months (range)	37.7 (0–51)

DoCR by IRC (N=155)



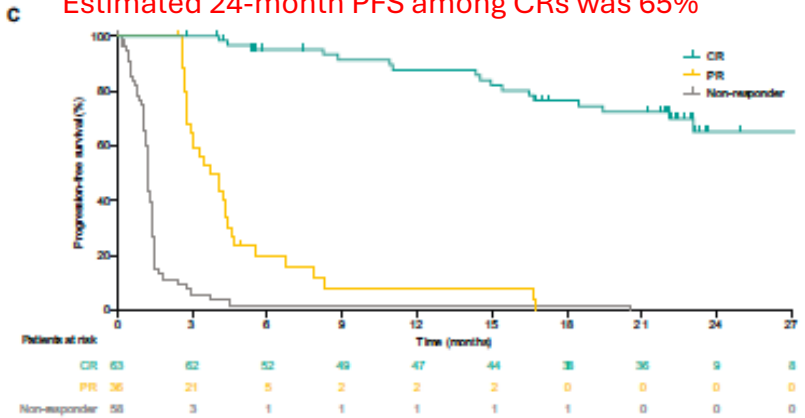
- Median time on study: 41.0 months (range: 0–52)

An estimated 56.4% of patients with a CR at any time remained in remission at 24 months

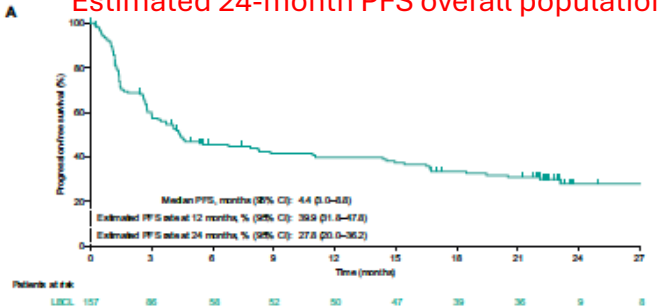
All responses in the table are based on the best overall response *Intention-to-treat population; †n=62. CI, confidence interval; NE, not estimable.

Epcoritamab in relapsed/refractory large B-cell lymphoma: 2-year follow-up from the pivotal EPCORE NHL-1 trial

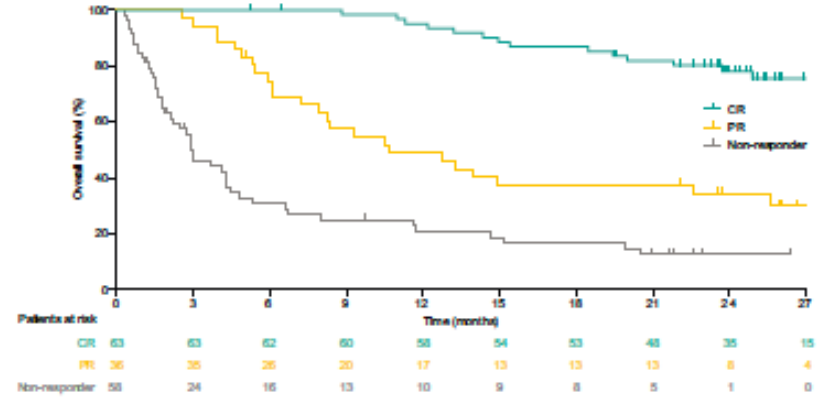
Estimated 24-month PFS among CRs was 65%



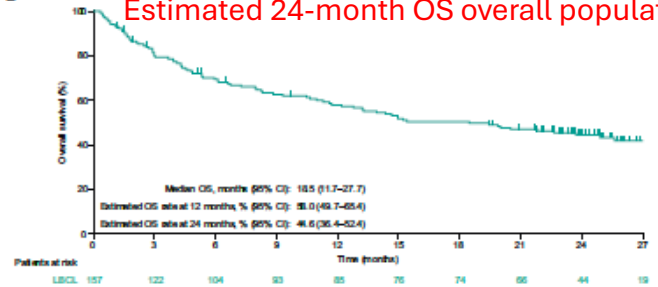
Estimated 24-month PFS overall population 28%



Estimated 24-month OS among CRs was 78%



Estimated 24-month OS overall population 45%



Thieblemont C., Leukemia 2024

Time from CAR-T infusion is a strong predictor of outcome of bispecific antibody therapy in relapsed/refractory large B-cell lymphoma

Results:

- Impact of relapse timing post-CAR-T on BsAb response:

Early relapse (≤3 mo. after CAR-T infusion)

29%/10% ORR/CRR	**2.2 mo./4.2. mo** mPFS/mOS

Intermediate relapse (4-6 mo. after CAR-T infusion):

54%/25% ORR/CRR	**3.7 mo./9.1 mo.** mPFS/mOS

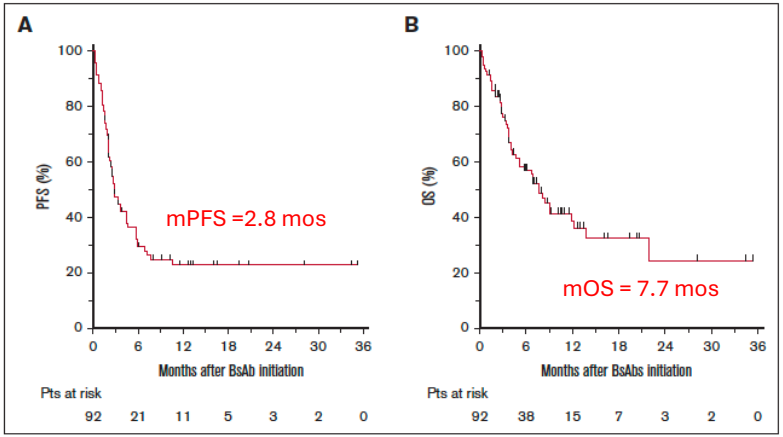
Late relapse (>6 mo. after CAR-T infusion):

60%/45% ORR/CRR	**10.5 mo./n. reached** mPFS/mOS

- Patients receiving BsAb as first salvage therapy and in non-early relapse post-CAR-T had better outcomes than those receiving BsAb in later lines of therapy (mPFS/mOS not reached vs. 2.7 mo/9.1 mo.)

- LDH, higher IPI, refractoriness to the last therapy predict poor outcome of BsAb following CAR-T failure

Survival outcomes of BsAbs after CAR-T failure



Shumilov E, Blood Advances, 2025

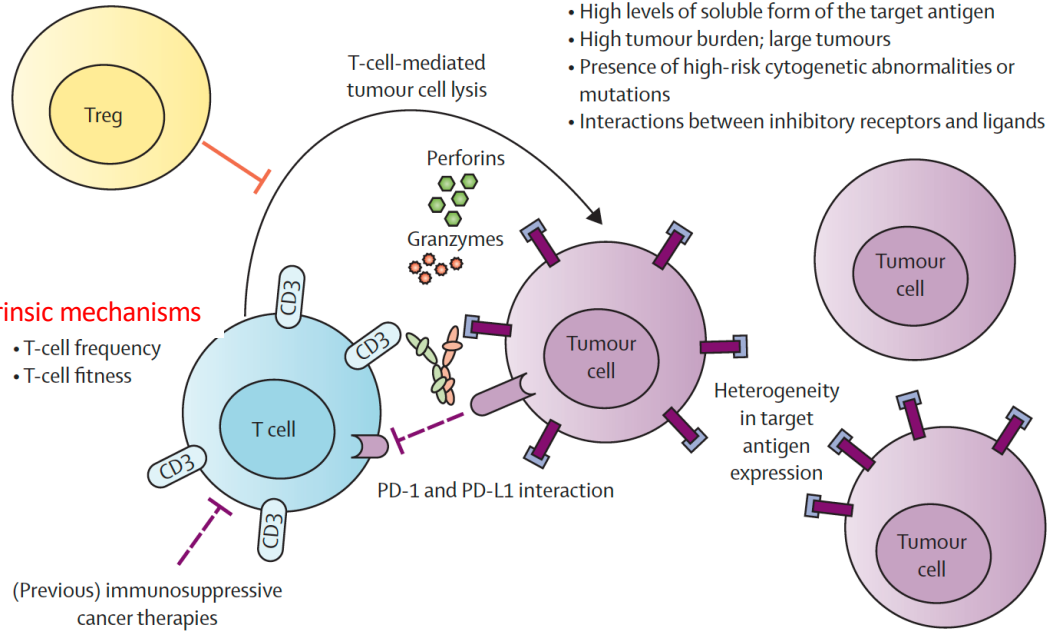
T-cell redirecting therapy – Mechanisms of resistance

Microenvironment Mechanisms

- Bone marrow stromal cells
- Immune suppressor cells (eg, Tregs)

Lymphoma cell-intrinsic mechanisms

- Target expression level at baseline
- Antigen loss or diminished antigen expression during treatment
- Tumour heterogeneity for target antigen expression
- High levels of soluble form of the target antigen
- High tumour burden; large tumours
- Presence of high-risk cytogenetic abnormalities or mutations
- Interactions between inhibitory receptors and ligands



T-Cell Characteristics

- Cumulative exposure to immunosuppressive anticancer drugs contributes to impaired T-cell fitness
- Chronic exposure to T-cell redirecting antibodies, may induce T cell exhaustion (proliferation, killing capacity, and cytokine secretion
- T cell exhaustion: inhibitory interactions with the tumour cells (eg, PD-L1)
- Insufficient T cell infiltration may prevent activation of a strong response

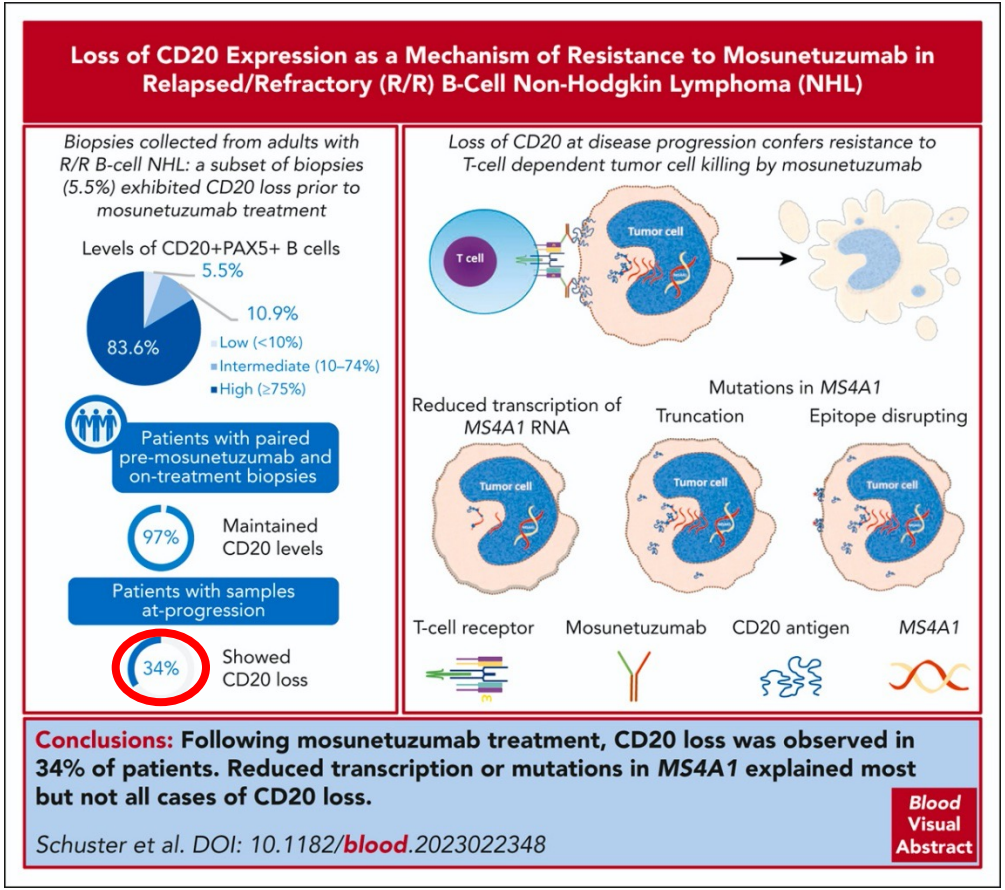
Immunosuppressive Microenvironment

- High levels of immunosuppressive cells (regulatory T cells, TAM, MDSC) and immunosuppressive molecules (TGF-β, IL-10) can inhibit T cell activity
- Bone marrow stromal cells also impair the activity of BsAbs against tumour cells by suppressing T-cell activation

Lymphoma-related features

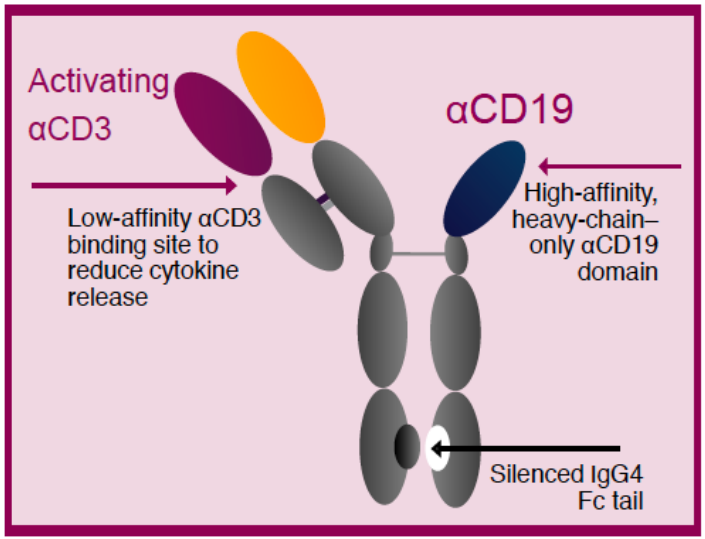
- Antigen downregulation or loss of expression of the target antigen (mutations)
- Selection of a pre-existing clone lacking target expression
- Heterogeneous antigen expression: Some tumor subclones may naturally express less of the target antigen, leading to immune escape
- Epitope masking or mutation: Structural changes in the antigen can prevent antibody binding.
- Genetic lesions in tumour cells associated with a lower response rate

ANTIGEN ESCAPE, predominantly related to acquired mutations in MS4A1 is a major cause lymphoma progression after treatment with the CD20xCD3 bispecific antibody mosunetuzumab



Schuster S., Blood, 2024,

AZD0486 Structure

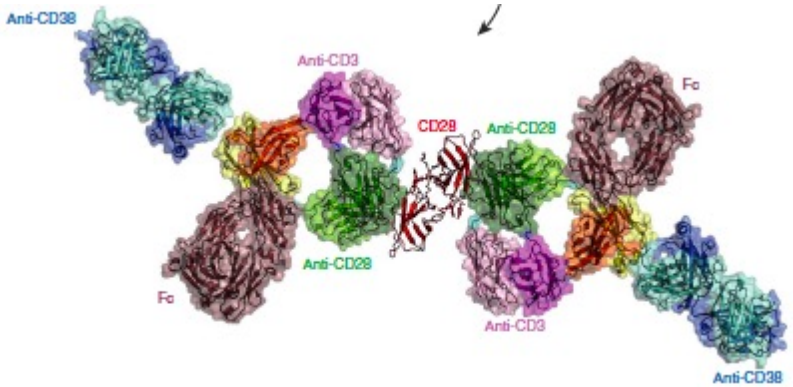


High Response Rates With Dose-Dependent Increases in OR and CR Rates Overall and by Prior CAR-T Status

	Overall (N=55)[a]			CAR-T Naive (n=22)			CAR-T Exposed (n=33)		
	n	ORR	CR Rate	n	ORR	CR Rate	n	ORR	CR Rate
2.4 mg	18	39%	22%	9	33%	22%	9	44%	22%
7.2 mg	19	47%	42%	5	80%	80%	14	36%	29%
15 mg	18	50%	39%	8	63%	38%	10	40%	40%

- Most responses were observed at first assessment (8 weeks)

Trispecific T-cell engagers (TriTEs) are advanced, engineered antibody constructs designed to enhance cancer immunotherapy by **binding to three distinct targets simultaneously**. By combining one T-cell engaging domain (e.g., CD3) with two other domains—which can target multiple tumor antigens or provide co-stimulation (e.g., CD28, 4-1BB)—TriTEs **improve tumor-specific cytotoxicity, overcome antigen escape, and reduce off-tumor toxicity**.



Acknowledgements

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