Meccanismi di immunoescape nei linfomi trattati con bispecifici

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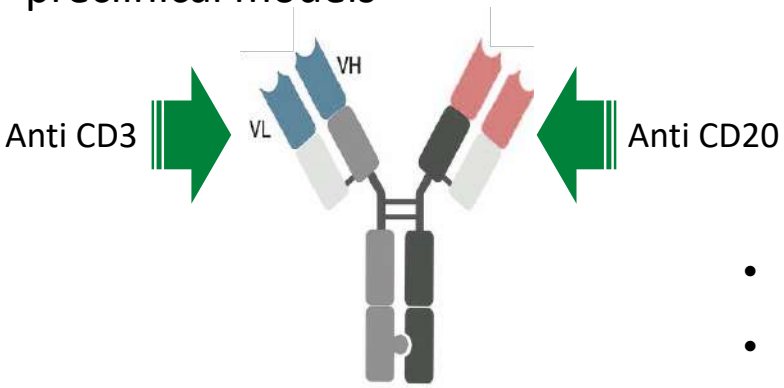
Disclosures of C. Carlo-Stella

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

Structural Features of the CD20xCD3 Bispecific Antibodies

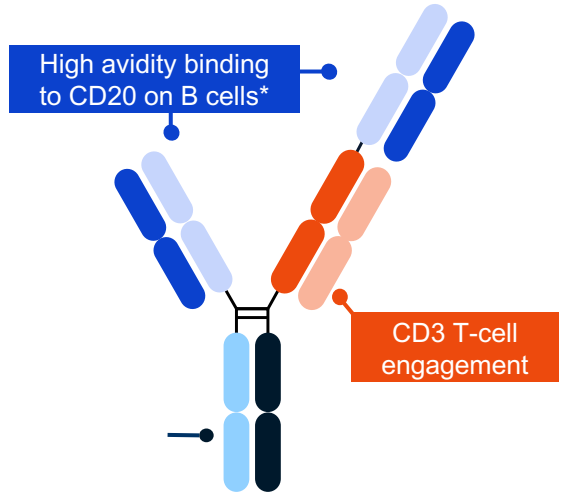
T-cell, binding, activation, expansion, T-cell mediated target cell death at low receptor occupancy

•*Monovalent binding (1:1 format)*
[epcoritamab, mosunetuzumab, odronextmab] reduces avidity and results in lower antitumour activity in preclinical models

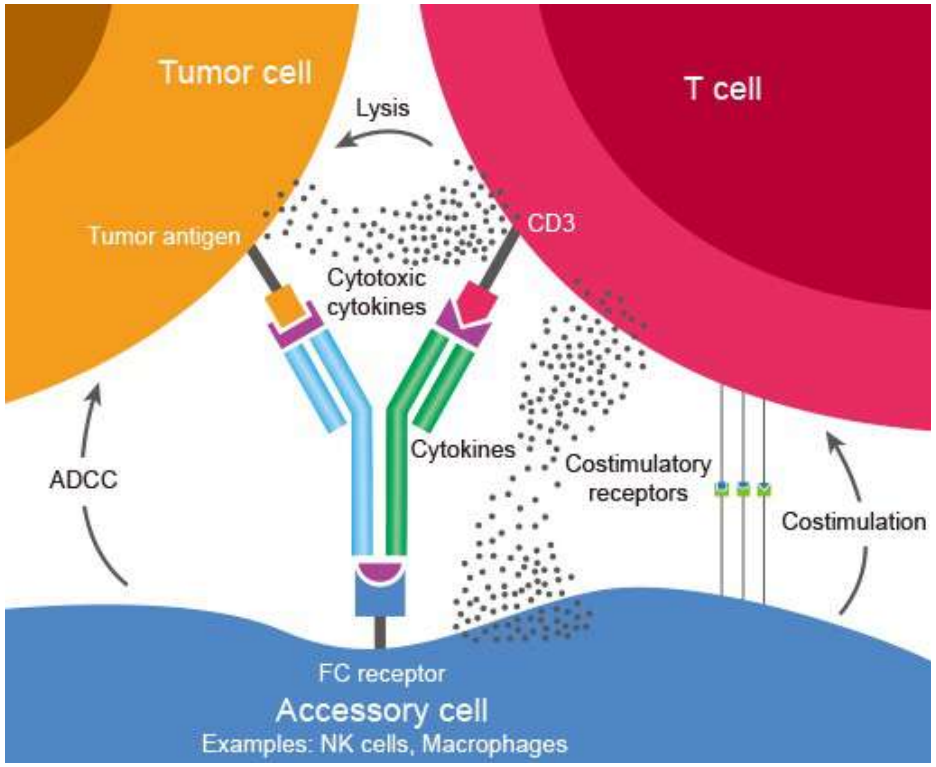


- CD3 on T-cells
- CD20 on B-cells (normal and malignant)
- Full length antibody
- Fc modifications and silencing
- Long half-life and reduced toxicity

•*Bivalent binding (2:1 format)*
[glofitamab] increases avidity binding and results in higher antitumour activity in preclinical models



Immune Synapse

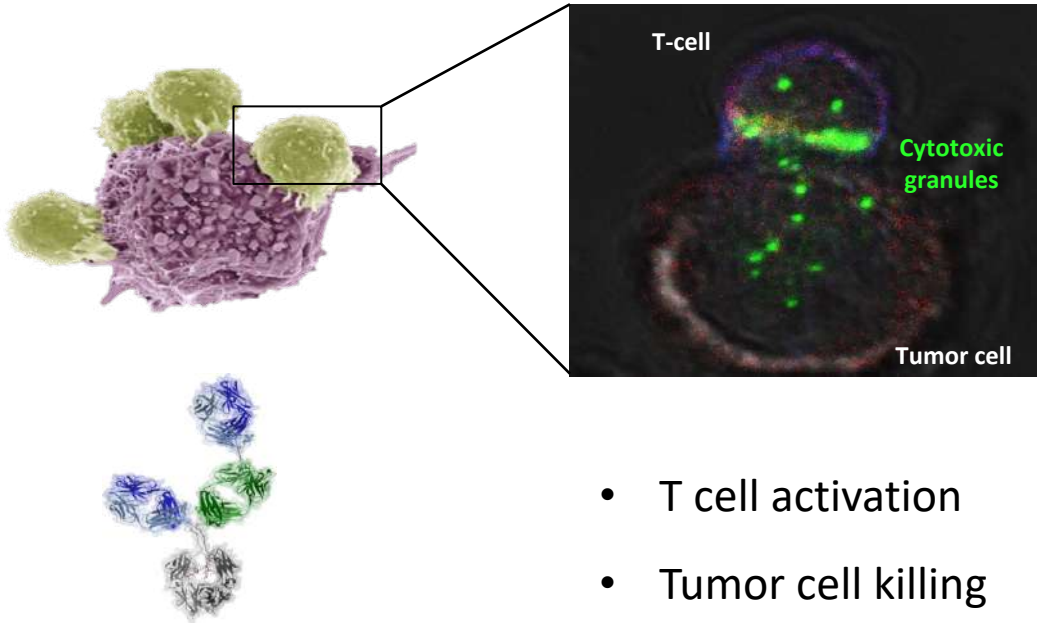


- *Simultaneous binding* to CD20 on tumor cells and CD3ε chain of the TCR on T cells results in the formation of **an immune synapse**
- T cell activation and release of perforins and granzymes result in **T cell-dependent killing of the tumor cell**.
- Both CD4+ and CD8+ T-cell subsets can eliminate 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

T-cell Bispecific Antibodies (TCBs)

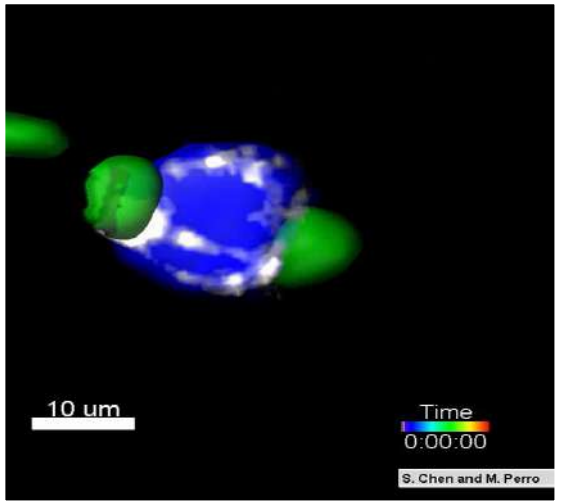
Highly potent molecules leading to T-cell-mediated killing of tumor cells

TCB mode of action



- T cell activation
- Tumor cell killing
- T cell expansion

Example of tumor cell killing by CD20-TCB



Tumor cell blue; CD8+ T cells green; TCB white

Bacac M, et al. Clin Cancer Res 2018;
Dickinson MJ et al., Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma, NEJM 2022;
Killock D, Engaging results with glofitamab in DLBCL, Nature Reviews Clinical Oncology 2022

Courtesy of Marina Bacac, Christian Klein and Pablo Umana

Response rates at RP2D – Pivotal data in 3L+ DLBCL

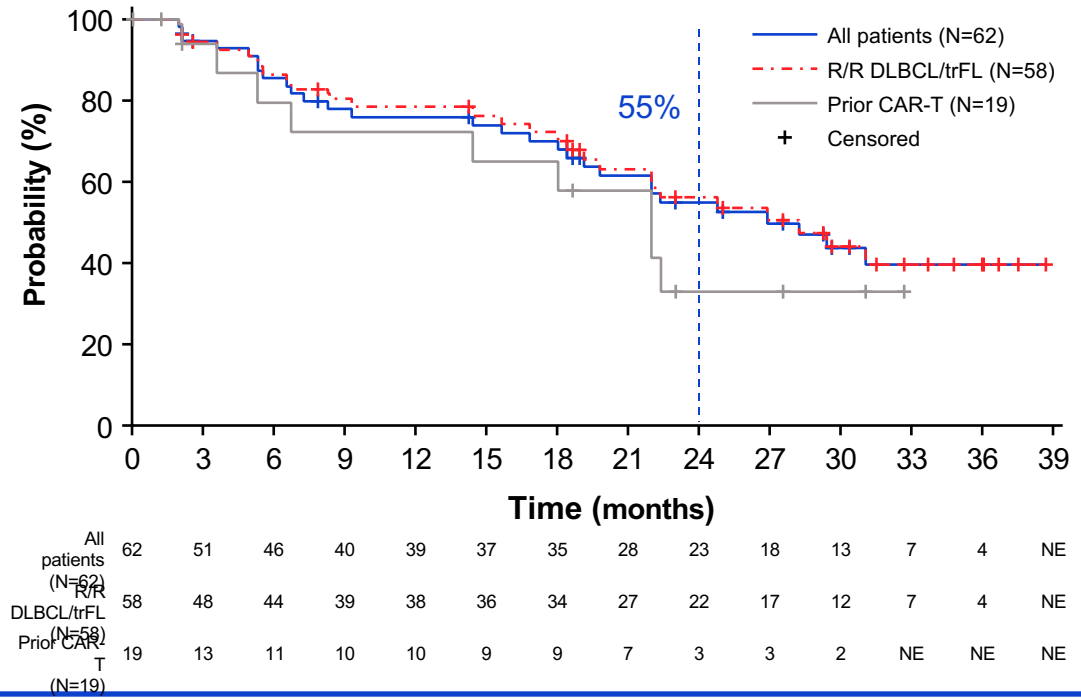
Characteristics	Glofitamab (n=155)*	Epcoritamab (n=157)**	Odronextamab*** (n=141)
CRR	61 (39.5%) [95% CI: 31.6%, 47.5%]	61 (39%) [95% CI: 31–47]	39 (31%)
ORR	80 (51.6) [95% CI: 43.5%, 59.7%]	99 (63) [95% CI: 55–71]	66 (52%)

*Dickinson M, NEJM 387:2220-2231, 2022; **Thieblemont C, JCO, 41:2238-2247, 2023; ***Ayyappan S, Blood 142: 436-38, 2023

Glofitamab CR Remained Durable

	All patients (N=155)*	R/R DLBCL/ trFL (N=132)[1†‡]	Prior CAR-T (N=52)[†]
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]	74 (56) [47.2–64.7]	26 (50) [35.8–64.2]
CR rate, n (%) [95% CI]	62 (40) [32.2–48.2]	58 (44) [35.3–52.8]	19 (37) [23.6–51.0]
Median DoCR, months (95% CI)	26.9 (19.8–NR)	28.3 (19.8–NR)	22.0 (6.7–NR)
24-month DoCR, % (95% CI)	55.0 (41.1–68.8)	56.2 (41.9–70.4)	33.1 (7.2–59.0)
Median CR follow-up, months (range)	29.6 (0–39)	29.6 (0–39)	23.0 (0–33)
Ongoing CRs, n/N (%)	34/62 (55)	32/58 (55)	10/19 (53)

DoCR by IRC



- Median time on study: 32.1 months (range: 0–43)

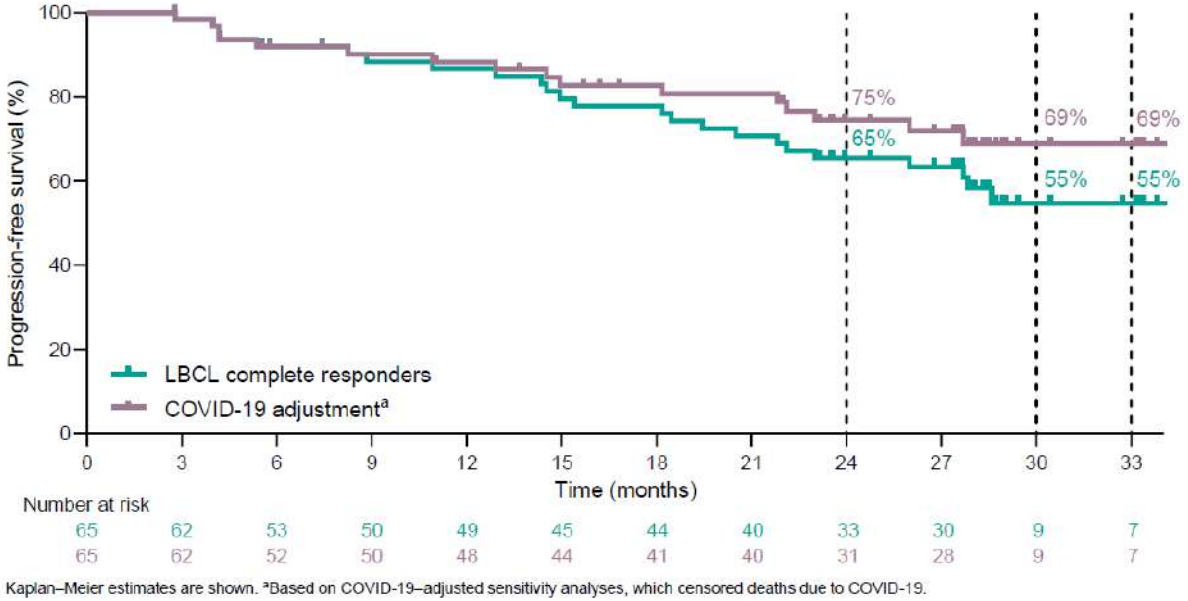
With 32 months median follow-up, glofitamab showed high response rates and durable remissions across subgroups

*Intent-to-treat population (DLBCL, trFL, HGBCL, and PMBCL); †Patients in this subgroup had similar baseline characteristics to the overall population; ‡Primary efficacy population reported in the glofitamab USPI, all patients received at least one dose of glofitamab. CI, confidence interval; NE, not estimable; NR, not reached; USPI, United States prescribing information.

1. COLUMVI USPI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761309s000lbl.pdf

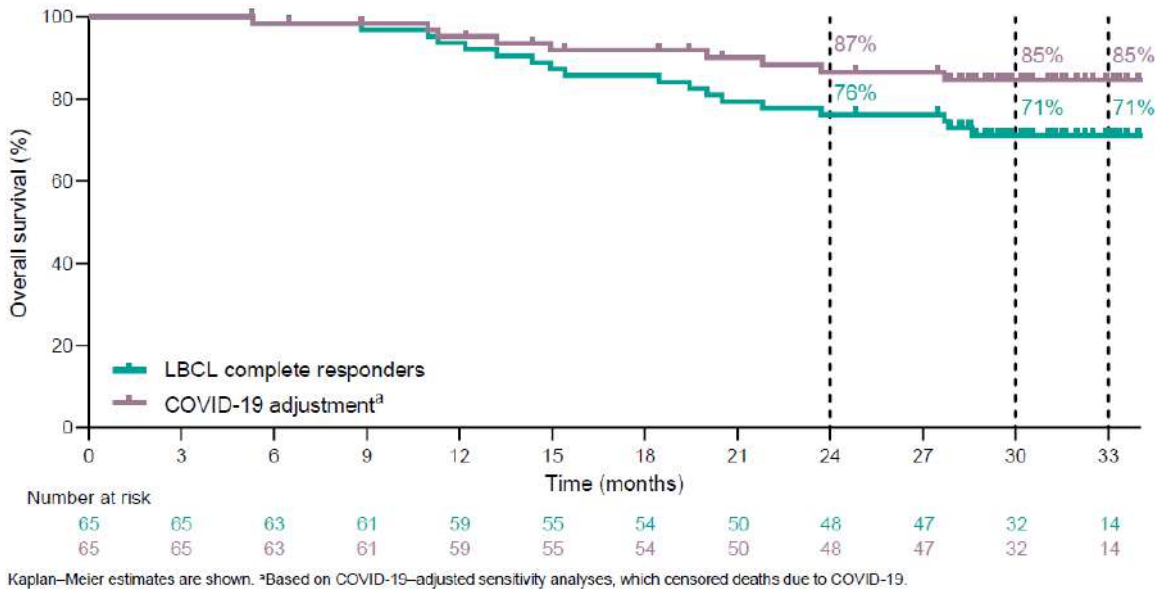
Epocoritamab CR Remained Durable

PFS



Kaplan–Meier estimates are shown. [a]Based on COVID-19–adjusted sensitivity analyses, which censored deaths due to COVID-19.

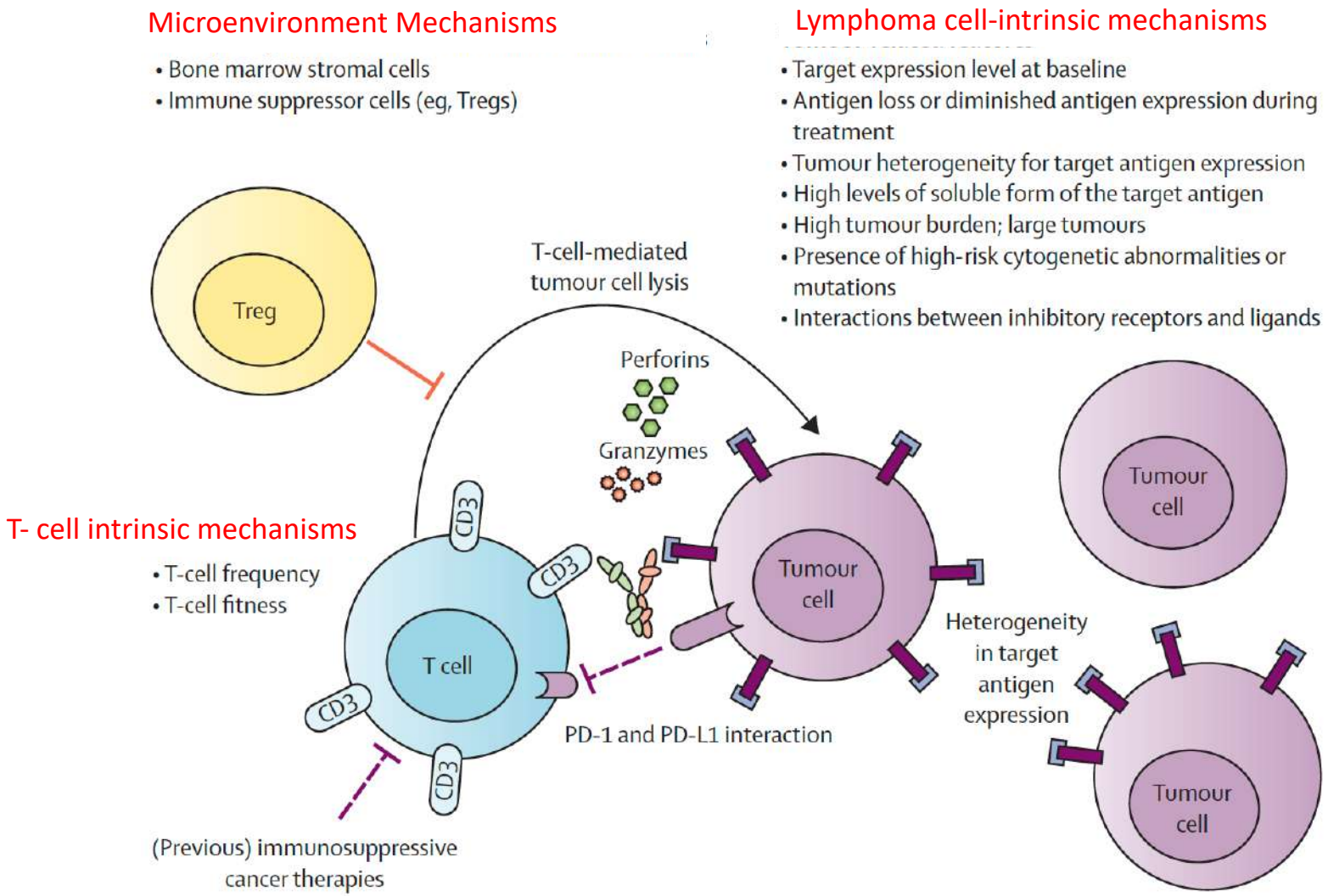
OS



Kaplan–Meier estimates are shown. [a]Based on COVID-19–adjusted sensitivity analyses, which censored deaths due to COVID-19.

Thieblemont C. et al. P1151, EHA 2024

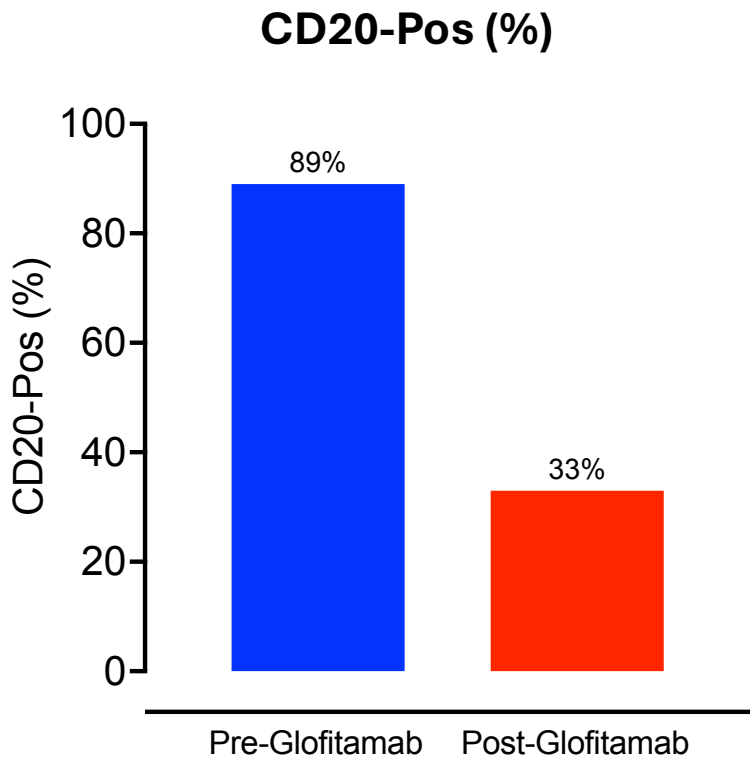
T-cell redirecting therapy – Mechanisms of resistance

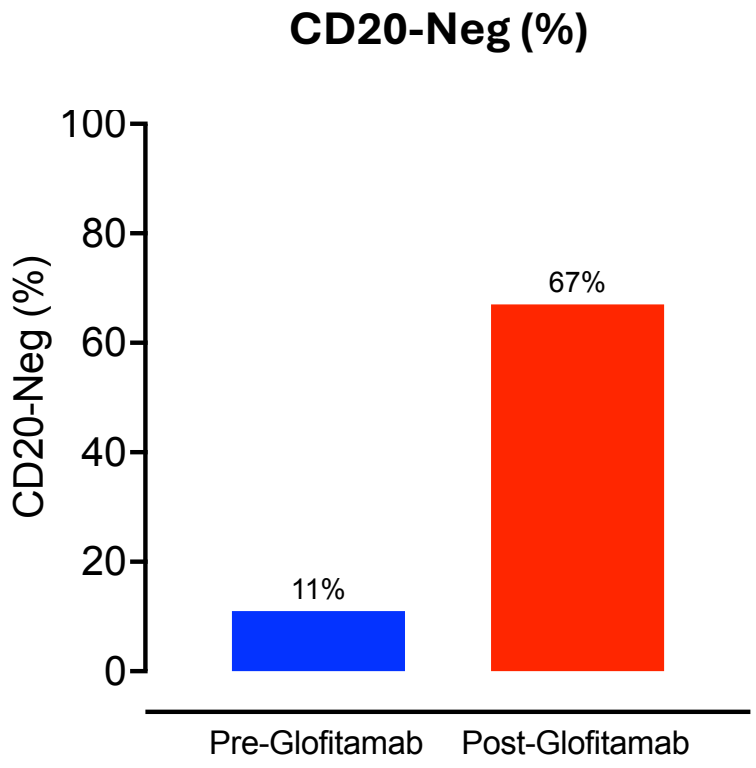


Lymphoma-related features

- 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

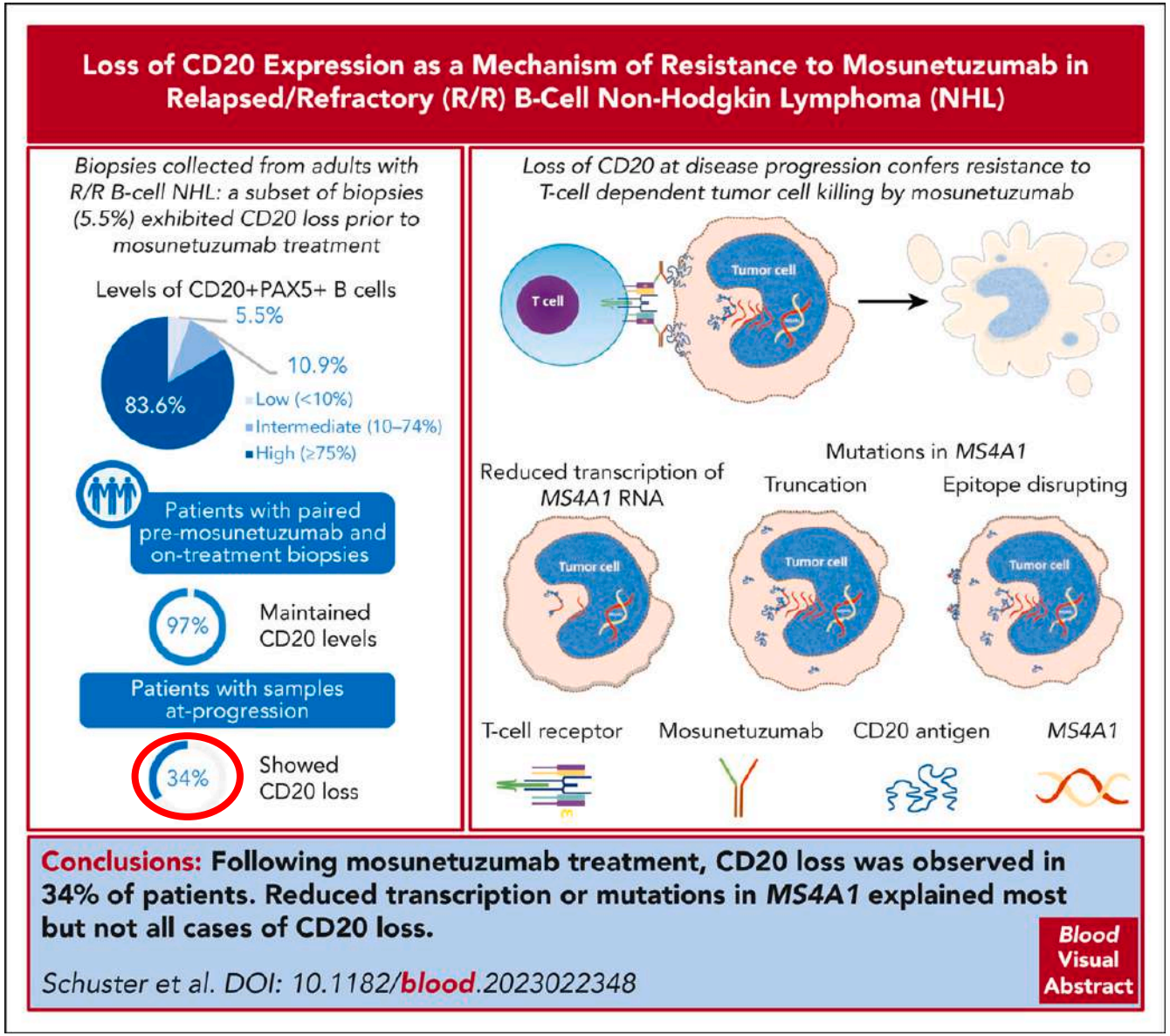
CD20 status before glofitamab and at relapse/progression Paired Biopsies





Grigg et al, BJH, 2024

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



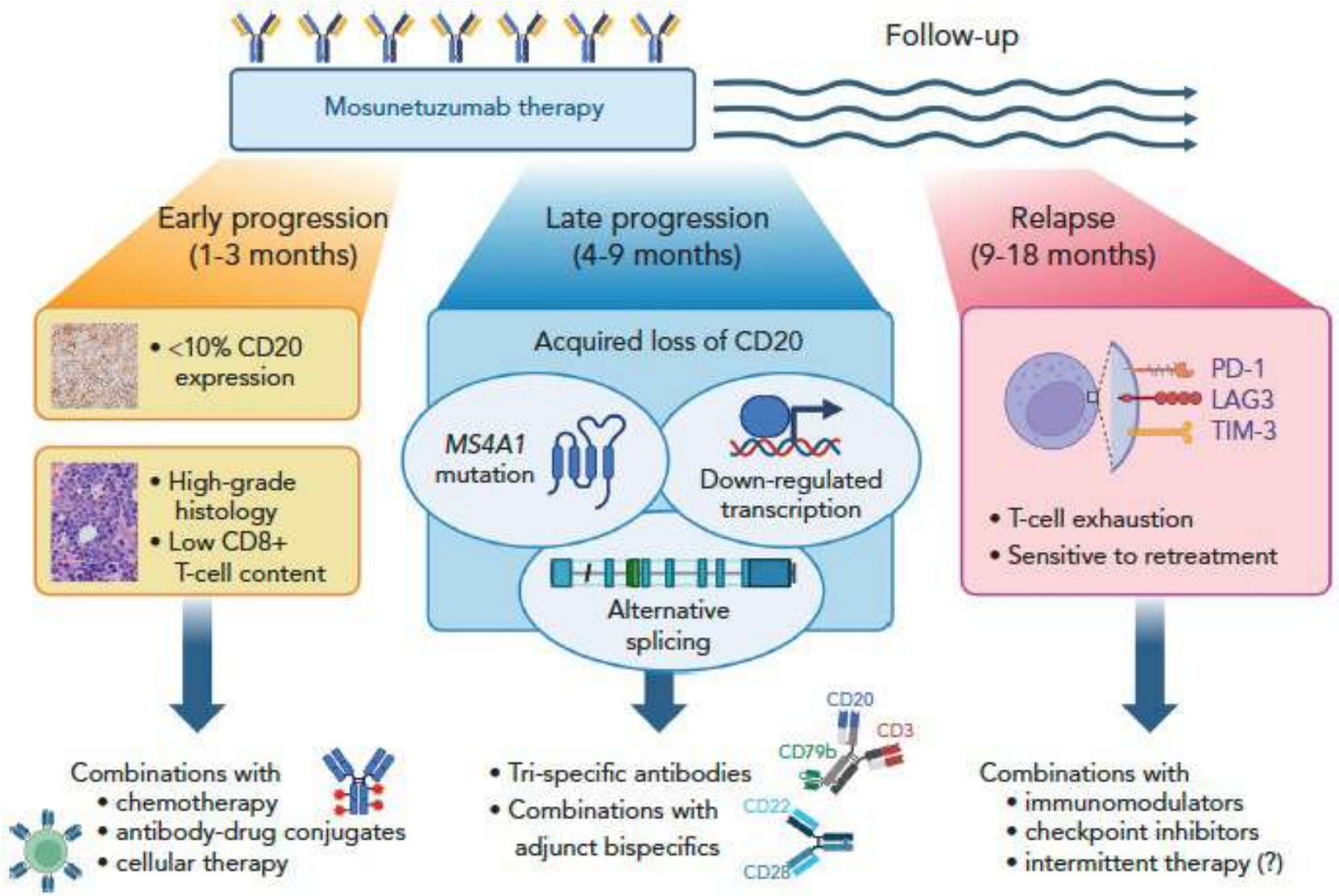
Schuster S., Blood, 2024,

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



50%of pts

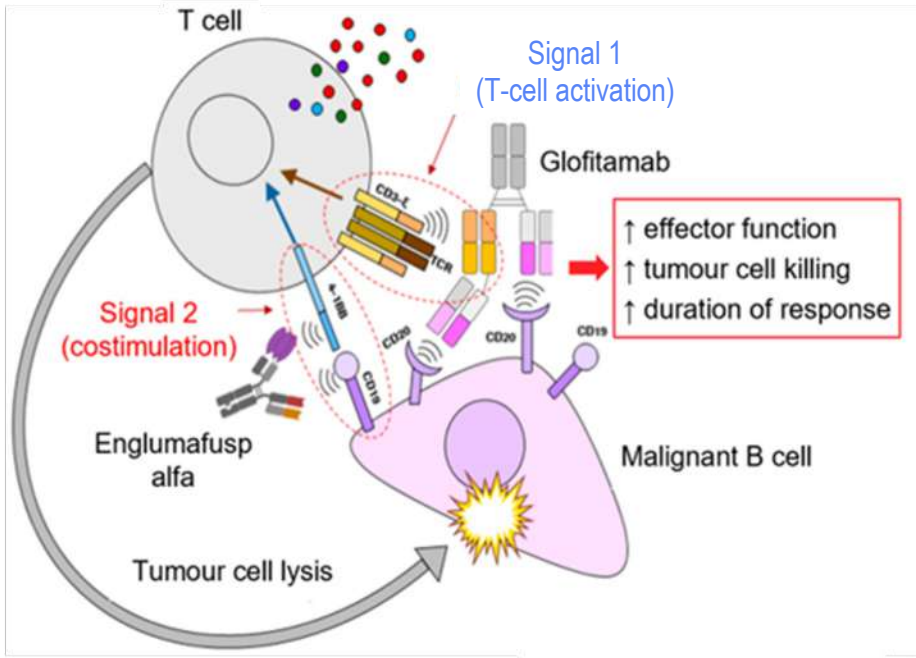
33%of pts

Olszewski A. Blood 2024

Background

- Englumafusp alfa (CD19x4-1BBL costimulatory bispecific antibody-like fusion protein)[1]
  - targets B cells (CD19) and immune cells expressing 4-1BB
  - elicits strong costimulatory signal (signal 2) that augments and prolongs T-cell activity, and has the potential to increase anti-tumour activity
- Glofitamab (CD20xCD3 T-cell-engaging bispecific antibody)[2]
  - targets malignant B cells (CD20) and activated T cells (CD3) (signal 1)
  - significant single-agent activity in R/R NHL[3–5]
- Ongoing Phase I study (BP41072*) is evaluating englumafusp alfa in combination with glofitamab in R/R B-cell NHL (B-NHL)[6]

Englumafusp alfa mechanism of action[1]



Aim: Present updated efficacy data for patients with R/R aggressive B-NHL (aNHL; n=83) and safety data for all patients with R/R B-NHL (N=134) in the dose-escalation part of the Phase I study

*NCT04077723; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory

1. Claus et al. Sci Transl Med 2019;11:eaav5989; 2. Bacac et al. Clin Cancer Res 2018;24:4785–97
3. Morschhauser et al. ASH 2021; 4. Dickinson et al. N Engl J Med 2022;387:2220–31
5. Phillips et al. ASCO 2024; 6. Dickinson et al. ICML 2023

Englumafusp alfa plus glofitamab shows promising activity in patients with R/R aNHL

Response rates across all dosing levels in evaluable patients with R/R aNHL

n (%)	n	BOR	CR
R/R aNHL			
3L+	70	46 (65.7)	37 (52.8)
2L+	83	56 (67.0)	47 (57.0)
R/R aNHL with prior CAR-T	42	26 (61.9)	20 (47.6)
R/R aNHL without prior CAR-T			
3L+	28	20 (71.4)	17 (60.7)
2L+	41	30 (73.2)	27 (66.0)
2L	13	10 (77.0)	10 (77.0)

Data cut-off date: 25 October 2024; BOR, best overall response; CR, complete response