3rd Meeting on T-Cell and NK-Cell Based Immunotherapies for Hematologic Malignancies, September 13-14, 2024

Bispecifics Resistance and Combinations in B-Cell non-Hodgkin Lymphoma

Lorenzo Falchi, MD

Assistant Attending, Lymphoma Service
Div. of Hematologic Malignancies
Dept. of Medicine

falchil@mskcc.org

Memorial Sloan Kettering Cancer Center

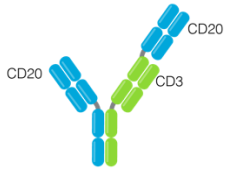
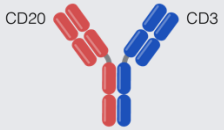
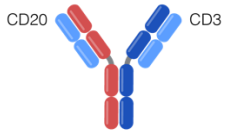
Disclosures

- **Research funding:** Roche, Genentech, Genmab, AbbVie, Innate Pharma
- **Consultancy:** Roche, Genentech, Genmab, AbbVie, Sanofi, Evolveimmune
- **Advisory board:** AbbVie, Genentech, ADC therapeutics, Seagen, Ipsen
- **Travel:** Genmab, AbbVie

Agenda

- Overview of CD20xCD3 bispecific antibodies (BsAb) and mechanisms of resistance (MoR)
- Individual MoR and strategies to overcome:
  - Antigen loss
  - T-cell dependent mechanisms
  - Other

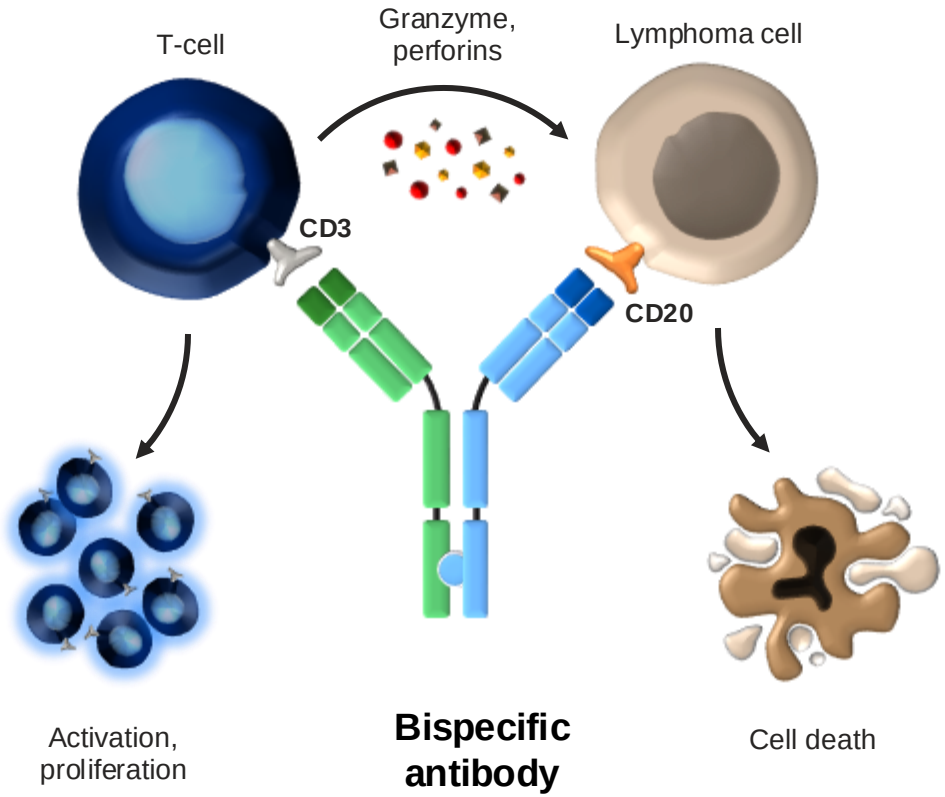
Overview of CD20xCD3 bispecific antibodies

Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio	Approved indication(s)*	ORR (CR) , %	PFS (months)
Mosunetuzumab		IgG1	Knobs-into-holes (different Fabs)	1:1	R/R FL	80 (60)	17.9
Glofitamab		IgG1	Head-to-tail fusion	2:1	R/R DLBCL	52 (39)	4.9
Epcoritamab		IgG1	Controlled Fab-arm exchange	1:1	R/R DLBCL R/R FL	63 (39) 82 (62)	4.4 15.4
Odronextamab		IgG4	Heavy chains with different affinity	1:1	R/R DLBCL R/R FL	52 (31) 80 (73)	not rep 20.7

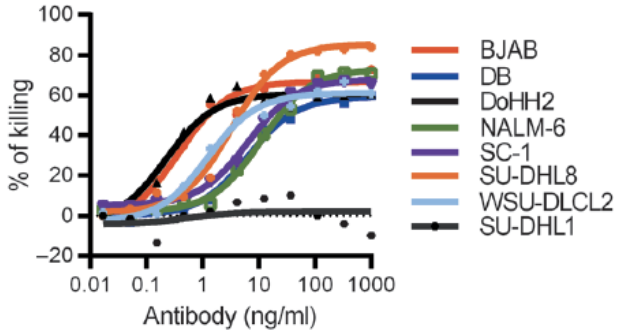
* Variably approved by the U.S. FDA, EMA and other regulatory agencies

Falchi L et al. *Blood*. 2023;141(5):467-480; Budde LE et al. Lancet Oncol. 2022;23(8):1055-1065; Dickinson MJ et al. *N Engl J Med*. 2022;387(24):2220-2231; Thieblemont C et al. J Clin Oncol 2023;41:2238-2247(2023); Linton K et al. Lancet Haematol 2024;11(8):e593-e605; Kim TE et al. Ann Oncol 2024 (ahead of print); Ayyappan S et al. *Blood* 2023; 142 (s1): 436.

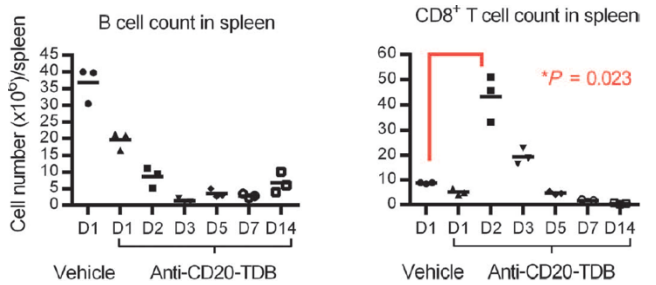
Basic mechanism of action of bispecific antibodies



Activity is target-dependent



Activity is conditional

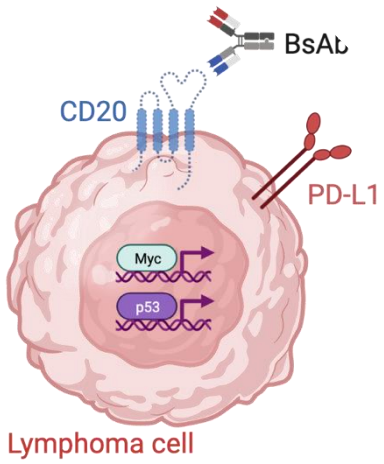


Matched time course of tissue B-cell and CD8+T-cell numbers after a single dose of mosunetuzumab in huCD20-huCD3 double-transgenic mice.

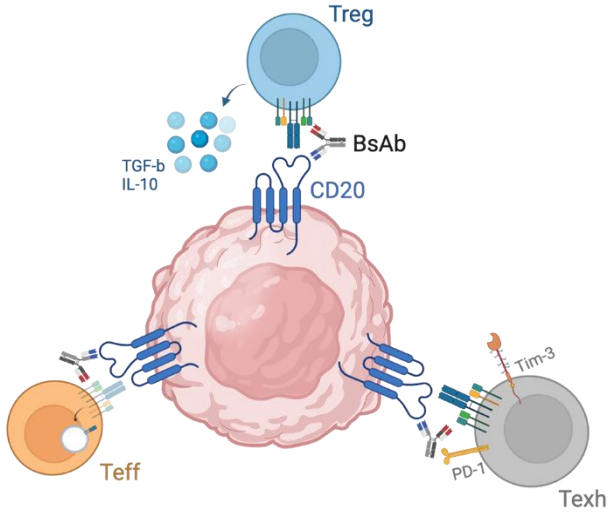
Sun LL et al. *Sci Transl Med*. 2015;7(287)287ra70.

Overcoming resistance to CD20xCD3 bispecific antibodies

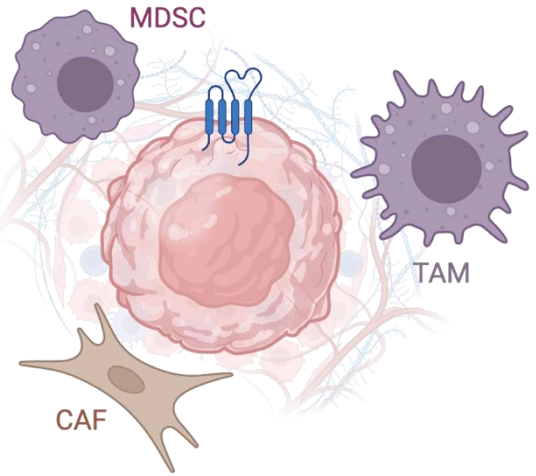
Tumor-intrinsic



T-cell-intrinsic



Tumor- and T-cell-extrinsic

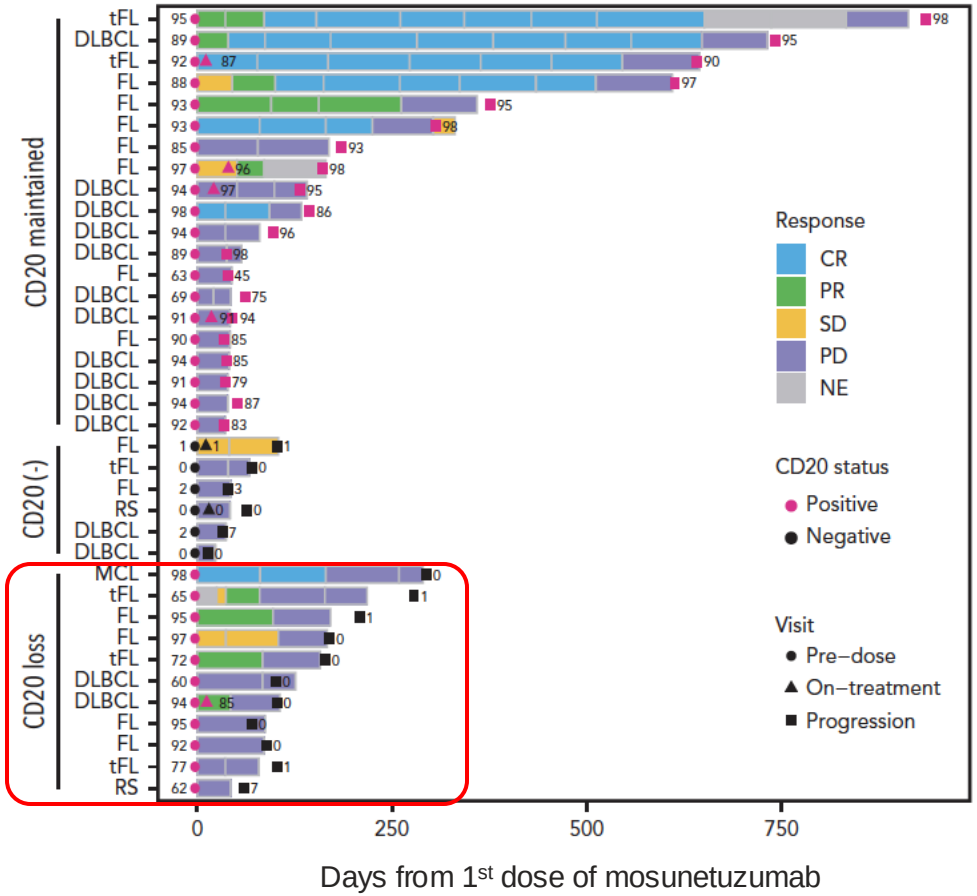


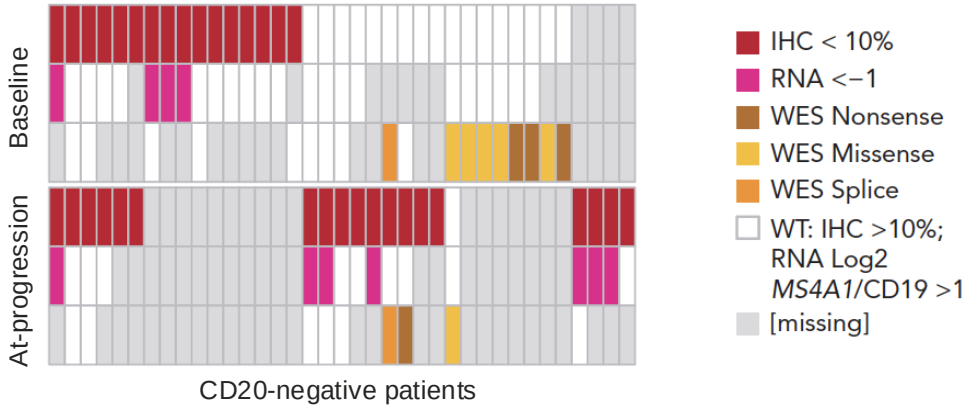
Modified from Falchi L et al. *Blood*. 2023;141(5):467-480.

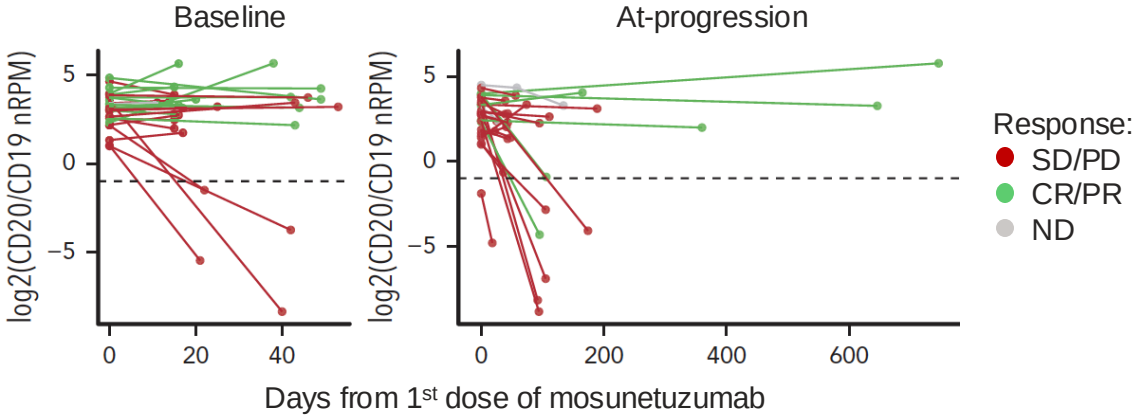
Mechanism of resistance #1

Antigen (CD20) loss

Mosunetuzumab in R/R FL: CD20 loss is frequent and associated with progressive disease

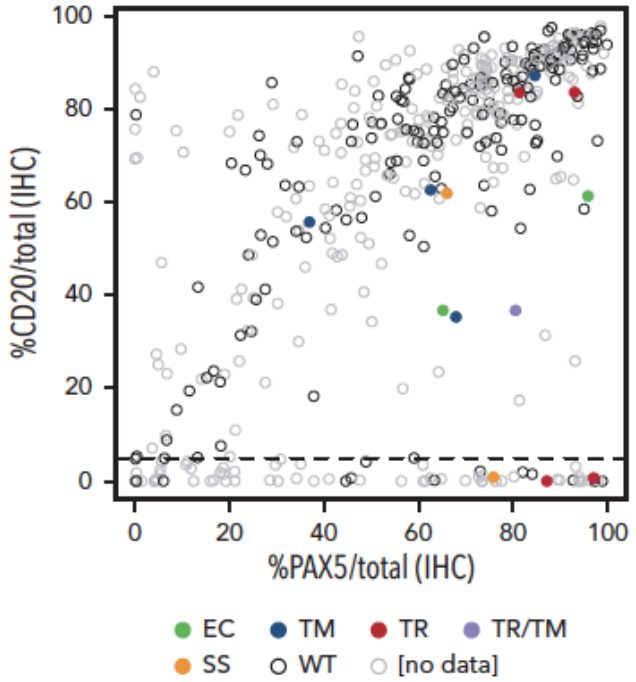




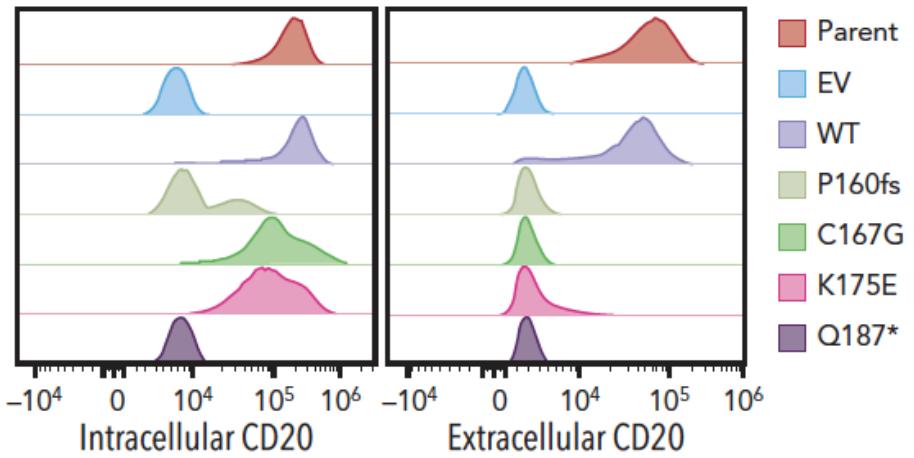


Schuster et al. Blood. 2024 Feb 29;143(9):822-832

Post-mosunetuzumab CD20 loss is only partly explained by *MS4A1* mutations



MS4A1 mutations were pre-existent in 10/154 patients with CD20 expressed by IHC in all cases

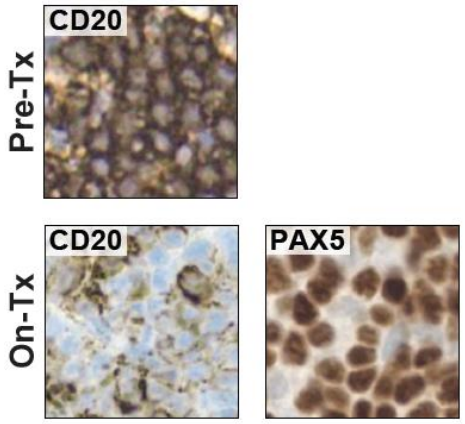


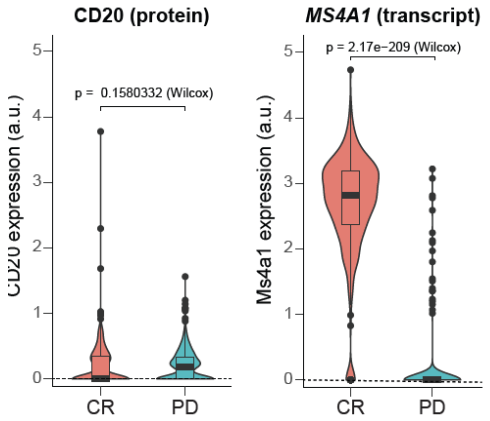
Detection of CD20 by flow cytometry in SU-DHL-16–engineered cell lines.

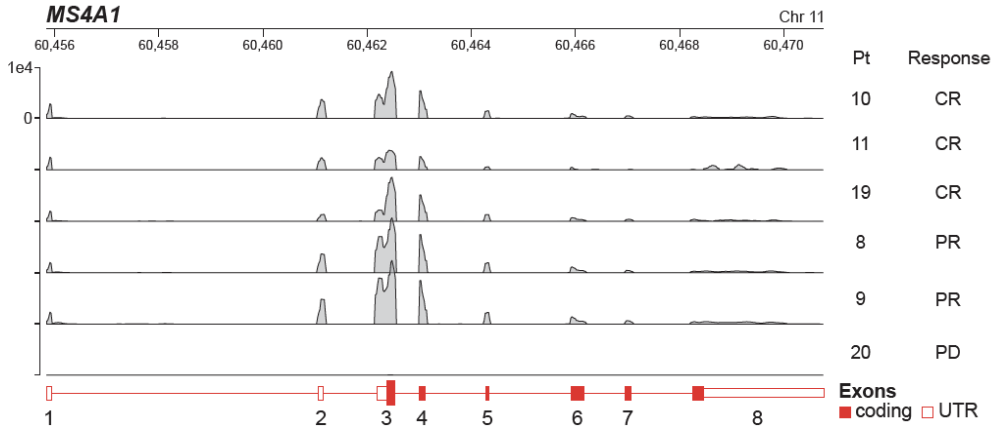
- Intracellular expression detected after permeabilization using anti-CD20 antibody targeting the C terminus (H-1, BD-561174),
- Extracellular expression detected using anti-CD20 antibody targeting ECL2 (2H7, BD-555623)

Schuster et al. Blood. 2024 Feb 29;143(9):822-832

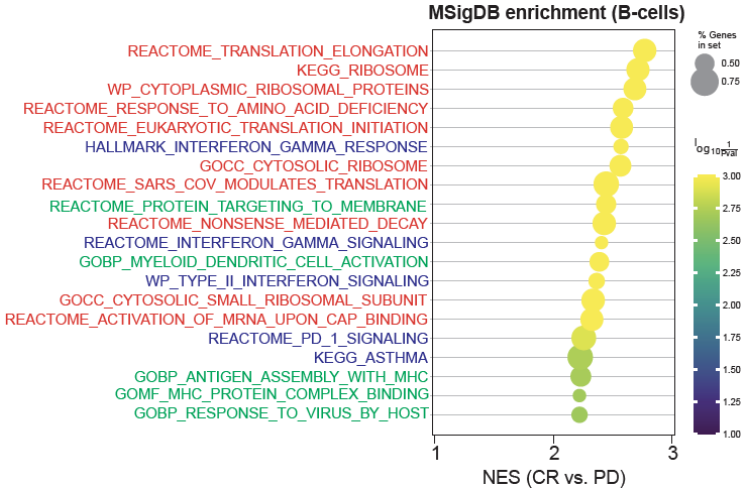
CD20 loss in patients with B-NHL treated with epcoritamab may be explained by post-transcriptional modifications of *MS4A1* and mechanisms differ in CR vs. PD

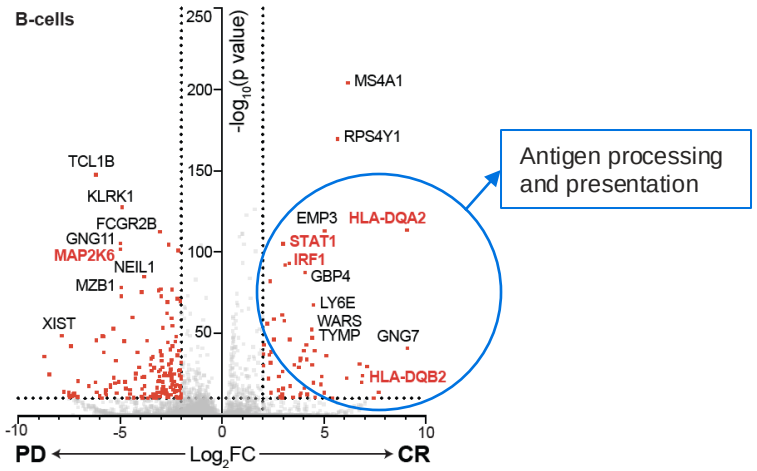






Ribosomal biogenesis and RNA stability



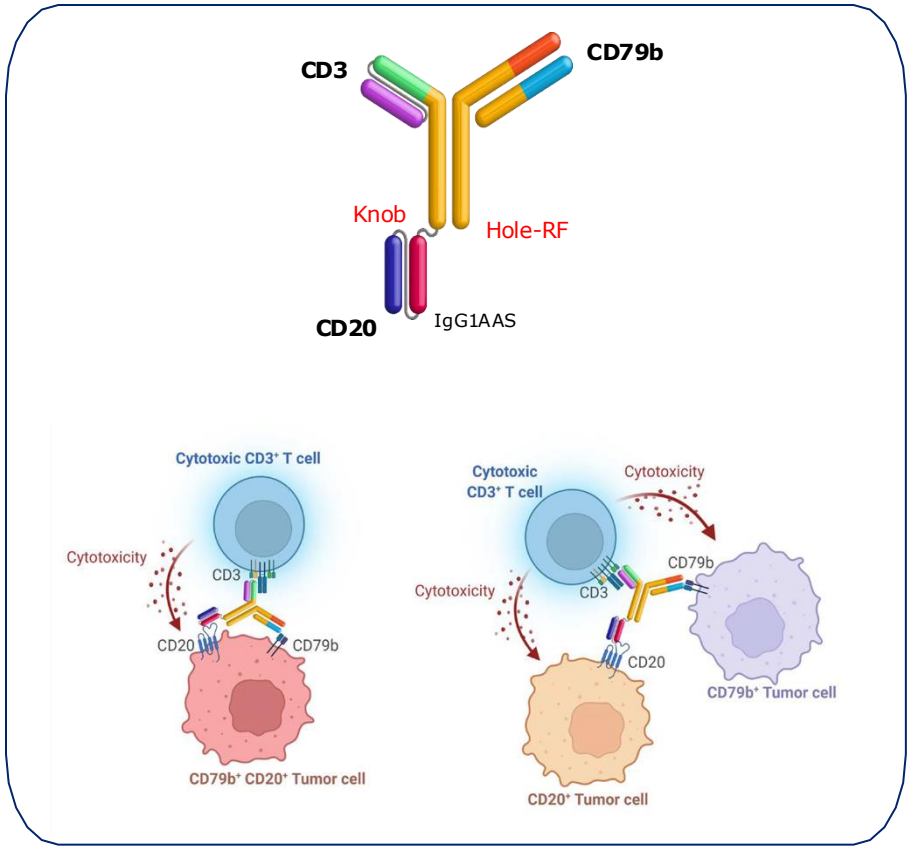


Antigen processing and presentation

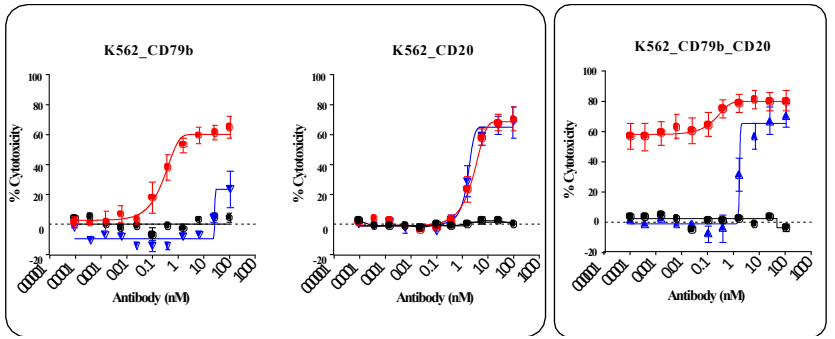
Falchi et al. *bioRxiv 2024*

Working around CD20 loss: JNJ-80948543 (CD79bxCD20xCD3) trispecific Ab

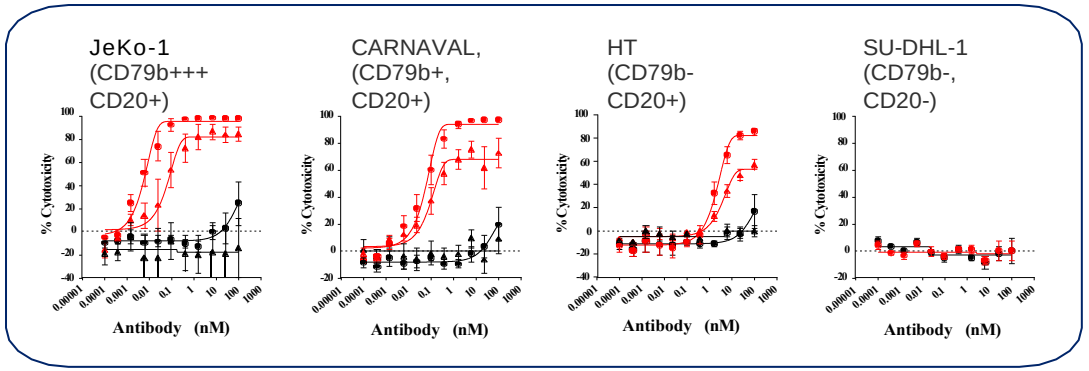
JNJ-80948543: Structure and MoA



Broader antigen targeting (T-cells from healthy donors)



Effect on Tumor Cells Expressing CD79b and/or CD20



T-cell Redirection Assays; E:T ratio 5:1

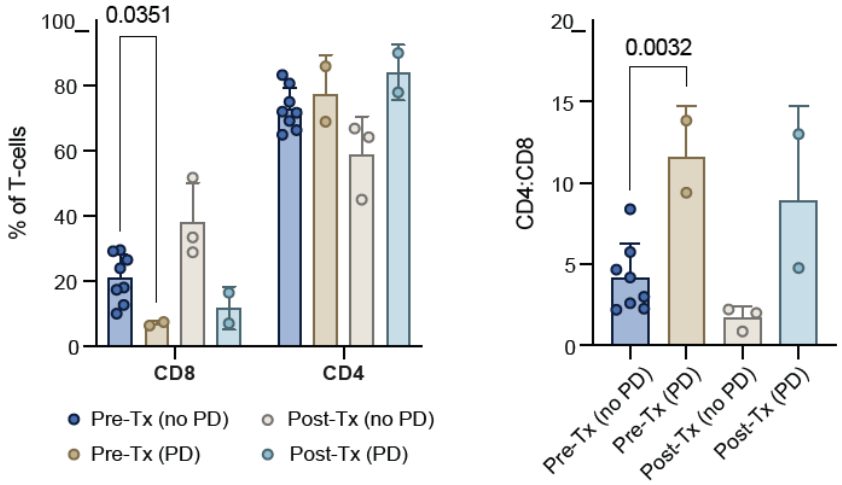
Note: No clinical data released to date.

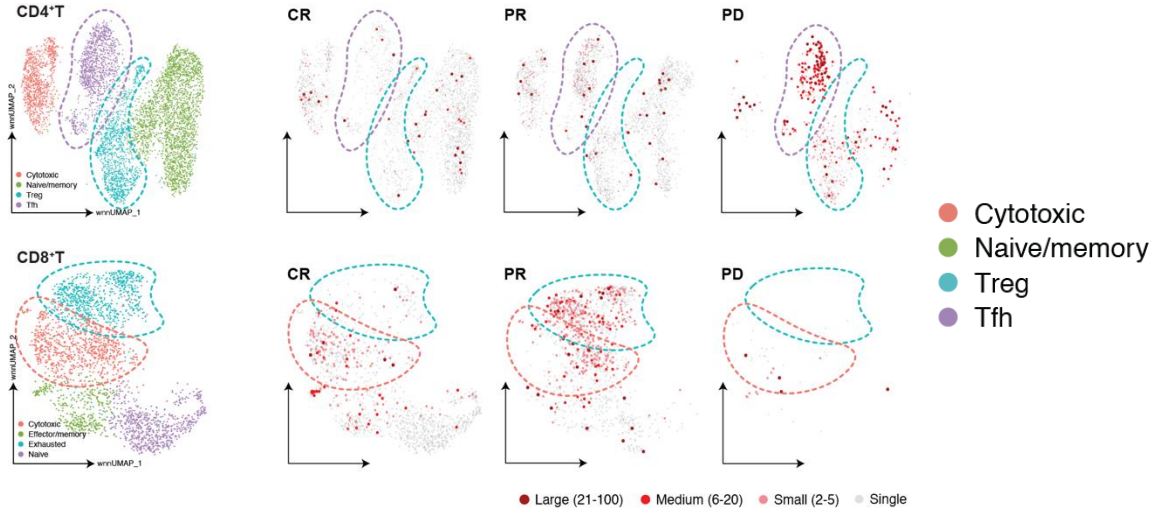
Kuchnio A et al. ASH 2022. Abstract 1342.

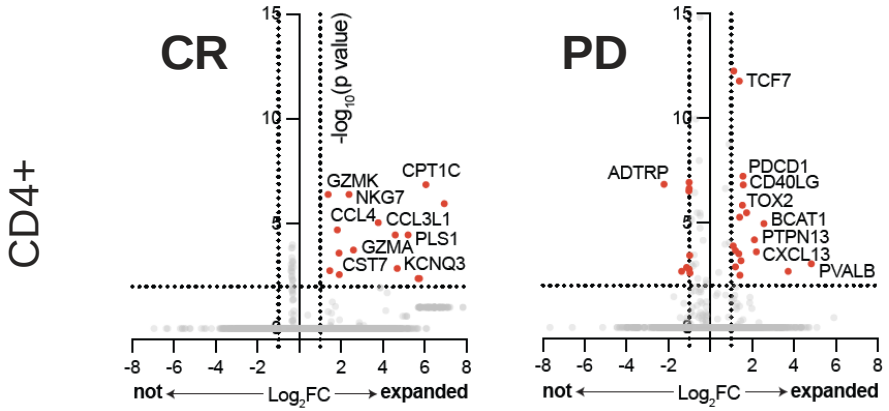
Mechanism of resistance #2

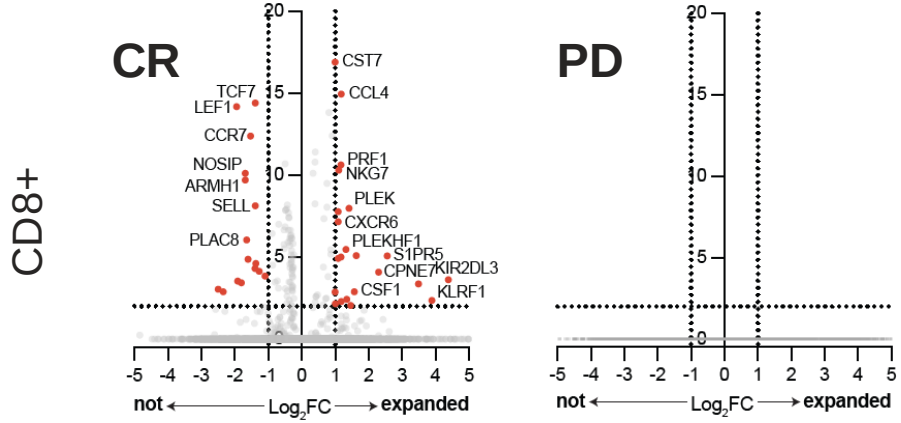
Qualitative and quantitative T-cell changes

On-treatment changes in T-cell subsets govern responses in patients with B-NHL treated with epcoritamab



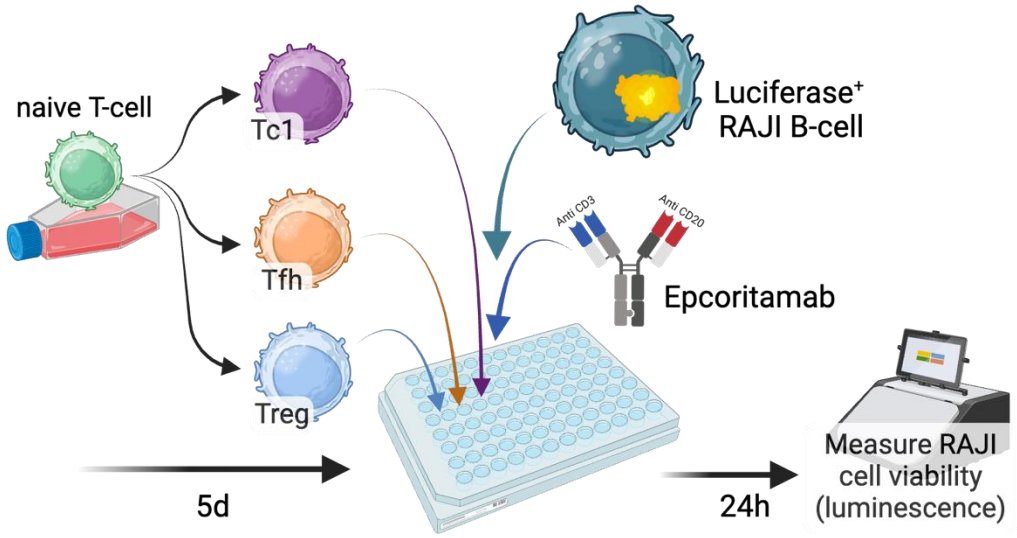


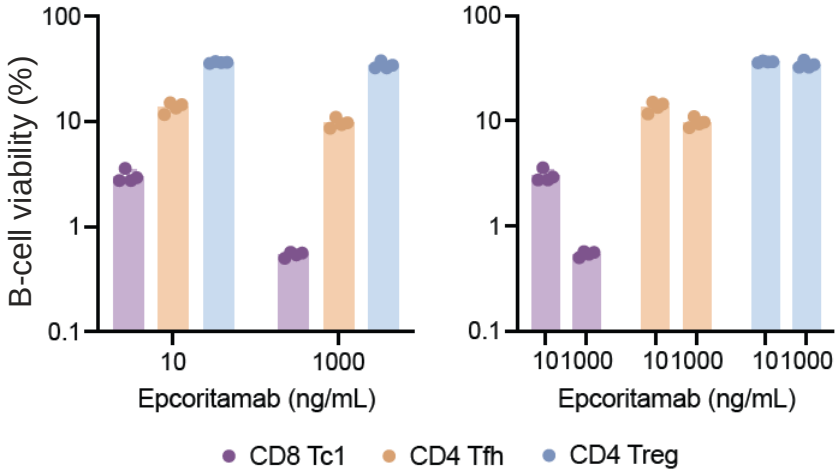




Falchi et al. *bioRxiv 2024*

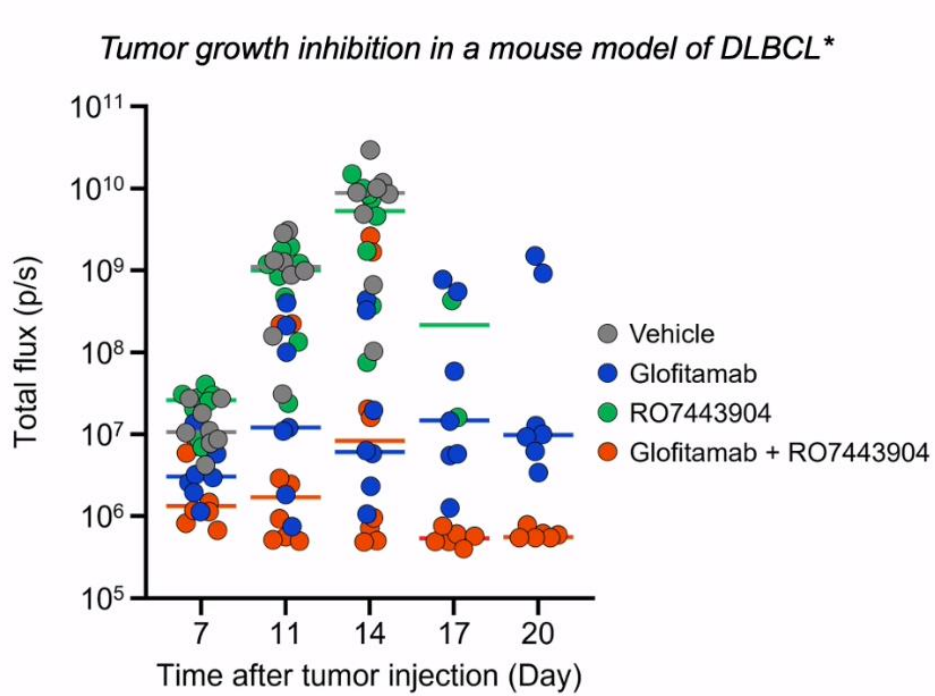
CD8+ cytotoxic T-cells specifically mediate epcoritamab-induced cell killing



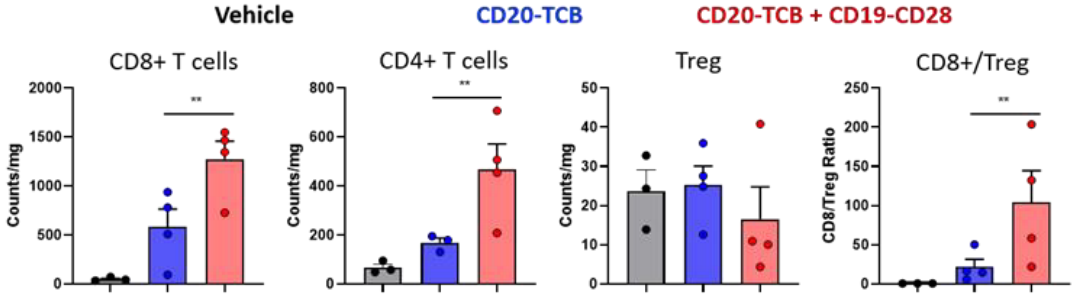


Falchi et al. *bioRxiv 2024*

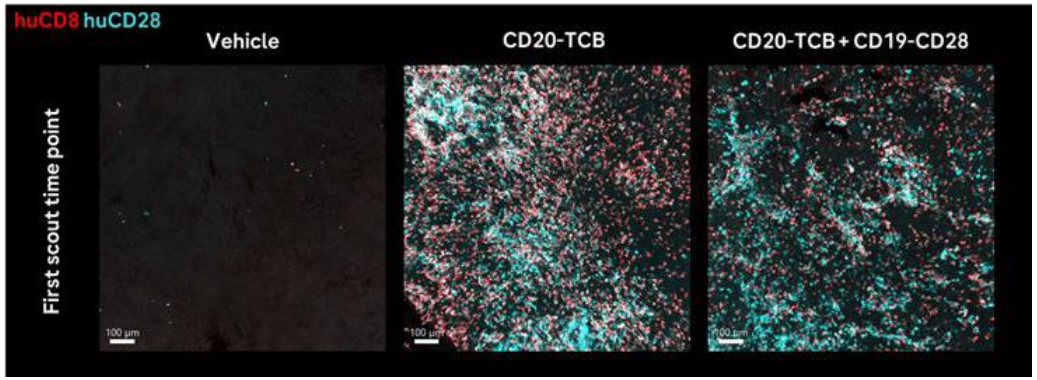
Restoring T-cell dysfunction: glofitamab + RO7443904 (CD19xCD28 co-stimulatory Ab)



Humanized NSG mice (7-8mice/group) implanted with WSU-DLCL2 Fluc lymphoma cells i.v. and treated once weekly i.v. with glofitamab (0.15mg/kg) or CD19-CD28 (1mg/kg) in monotherapy or with the combination starting on day 3. Tumor growth was recorded with BLI measurement.



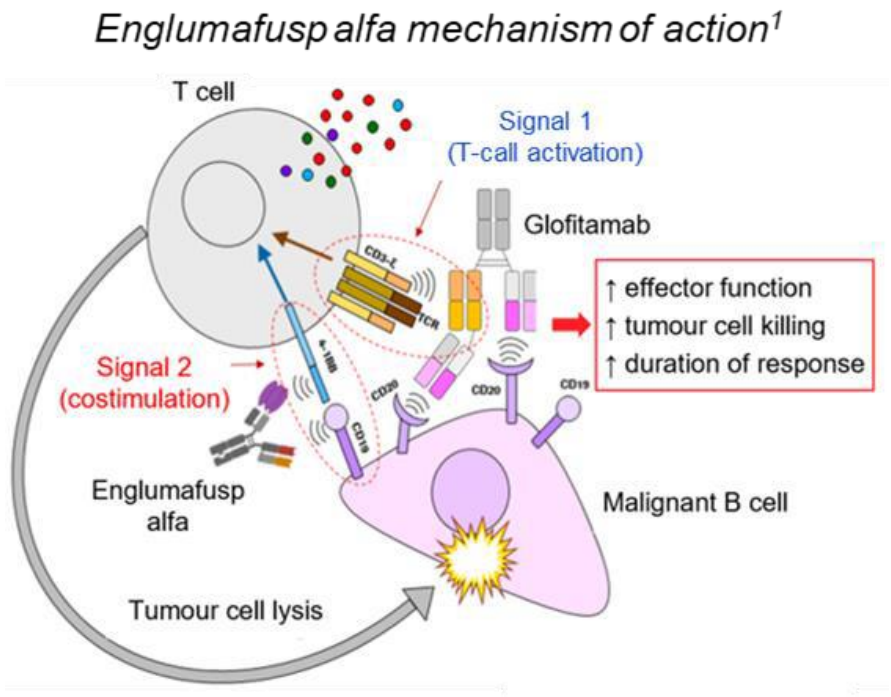
Humanized NSG mice were inoculated s.c. with WSU-DLCL2 lymphoma cells and received obinutuzumab followed by glofitamab (0.15mg/kg) alone or with CD19-CD28 (1mg/kg). Tumors were harvested 8 days later

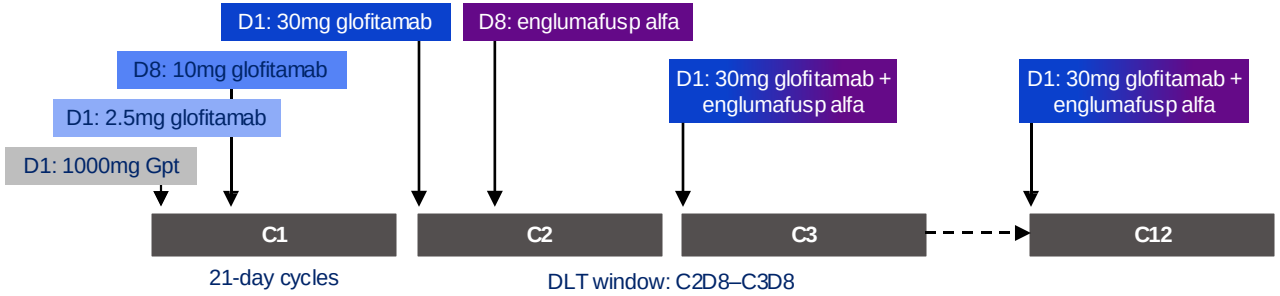


IF in tumors for CD8+CD28+ human T cell frequencies at 6 days after treatment with glofitamab alone or with CD19-CD28(1mg/kg)

Sam et al. ASH 2022. Abstract 1360 and Blood 2024

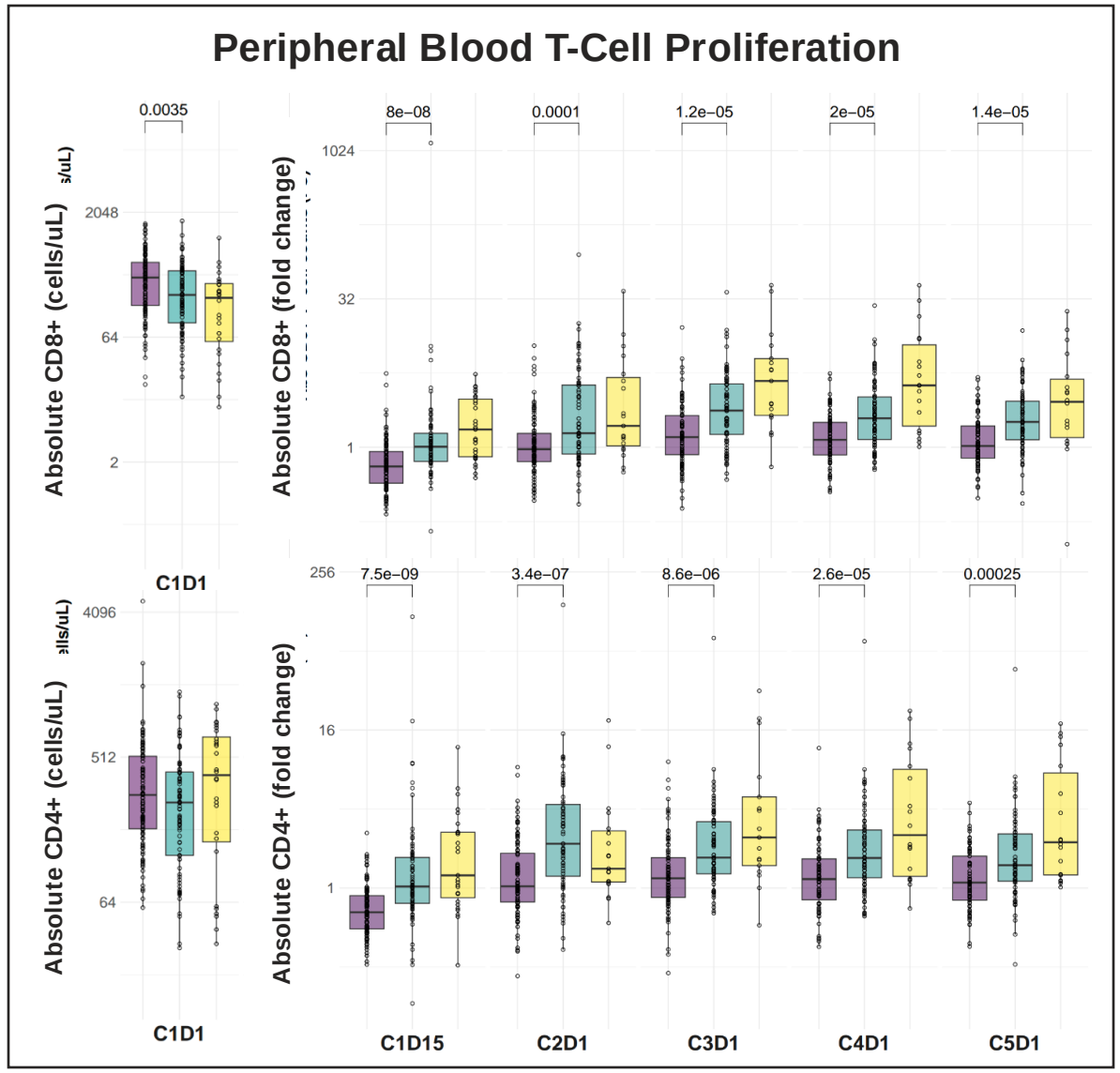
Englumafusp alfa (CD19x4-1BBL) + glofitamab in R/R aggressive B-NHL (N=83)

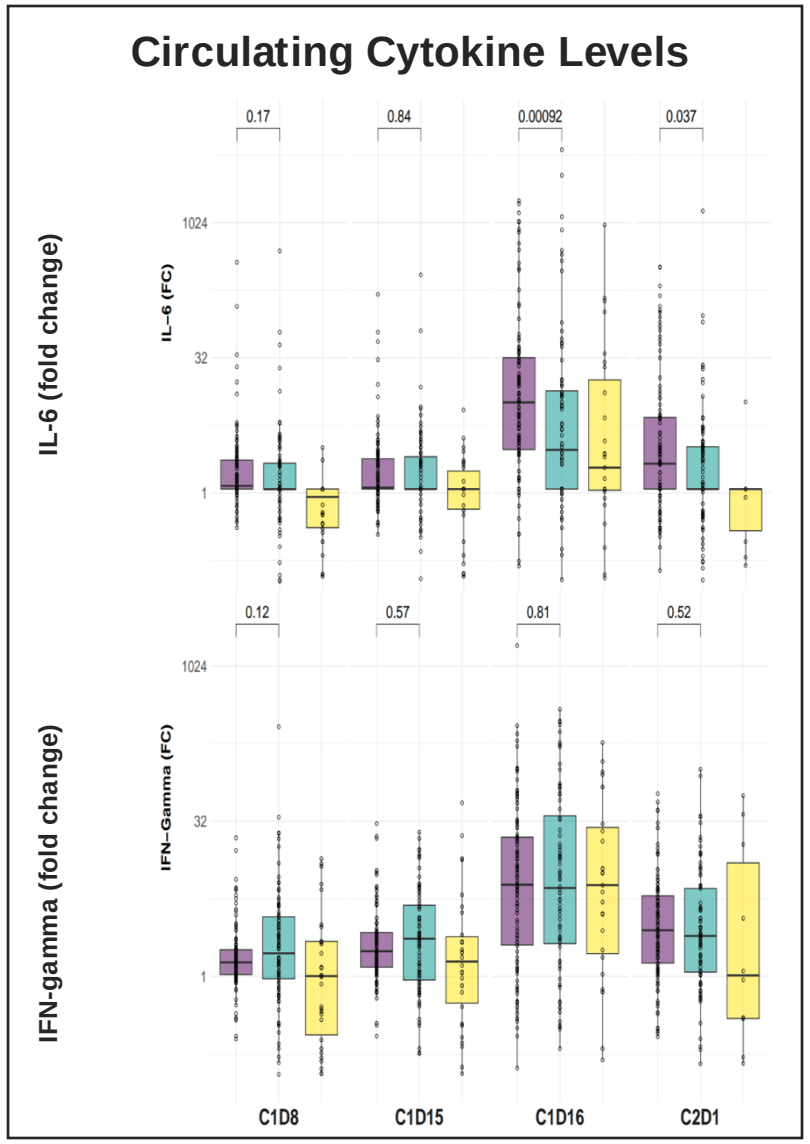




- **Population:** Median age 63; prior lines = 3 (1-8); refractory to CART N=35
- **Safety:** CRS 55% (G3 1%); infections 58% (G5 5%); neutropenia 25% (G3 20%)
- **Efficacy:** ORR 67%; CR 57%; CR post CAR-T 48%

Lenalidomide as rational combination partner for epcoritamab

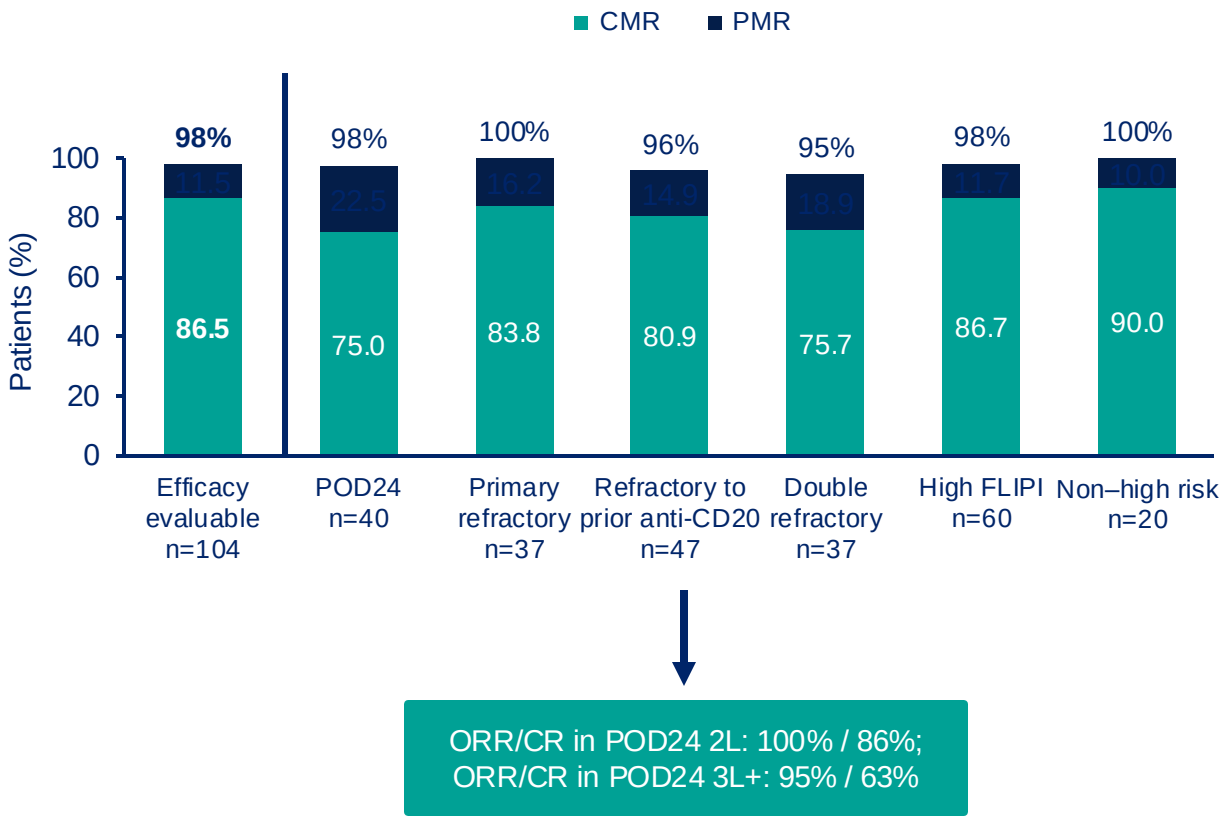




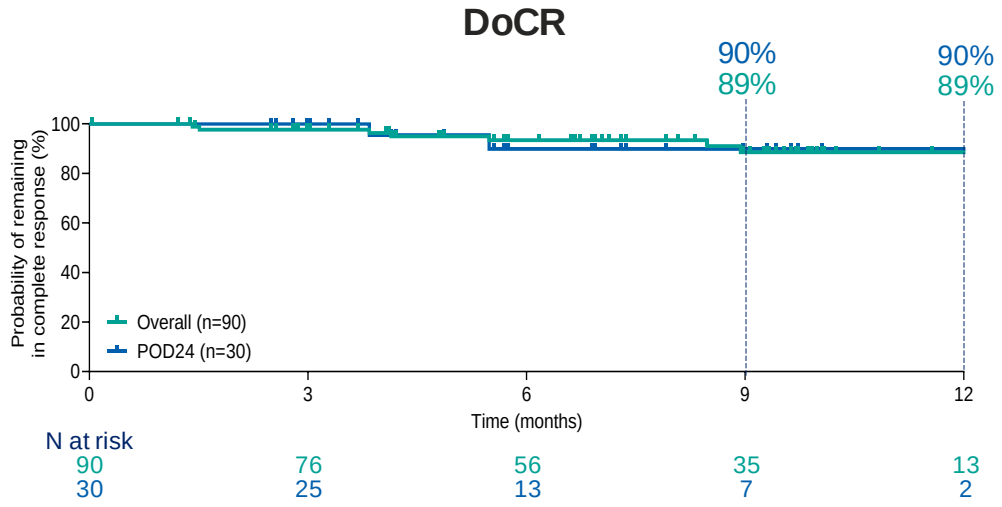
Epco (R/R FL) NHL-1 Exp, n=112
Epco+R² (R/R FL) NHL-2 Arm 2, n=86
Epco+ R² (ND FL) NHL-2 Arm 6, n=28

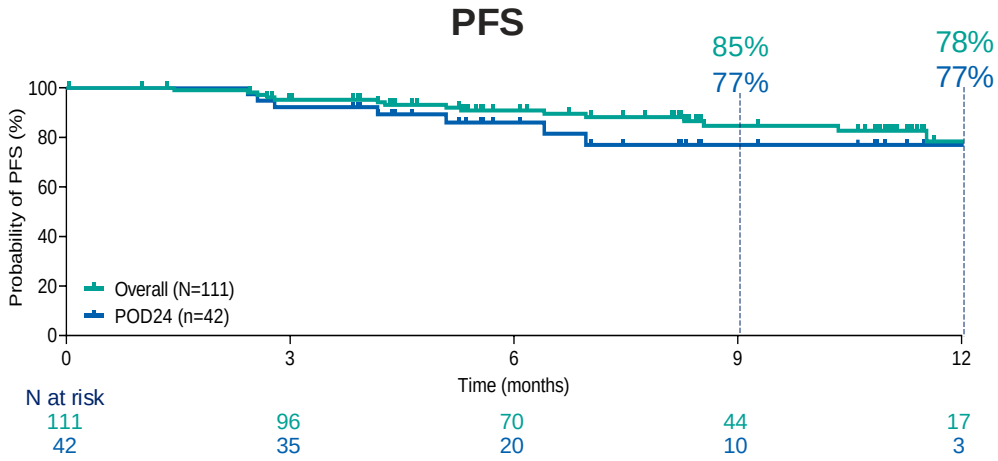
Si et al. AACR 2024

R²-epcoritamab in High-Risk R/R FL: Responses and Outcomes



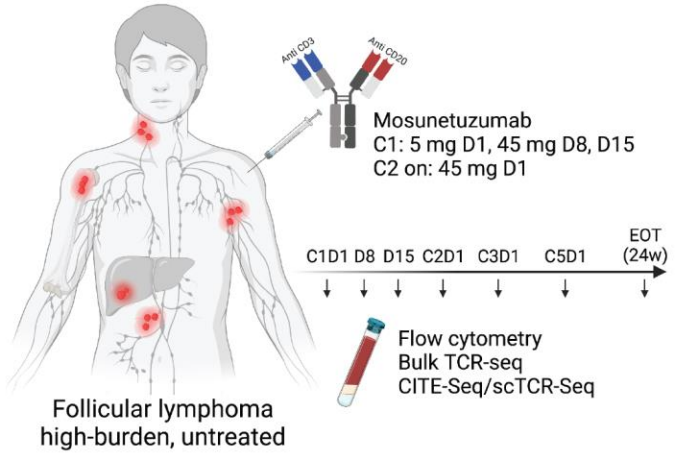
ORR/CR in POD24 2L: 100% / 86%;
ORR/CR in POD24 3L+: 95% / 63%

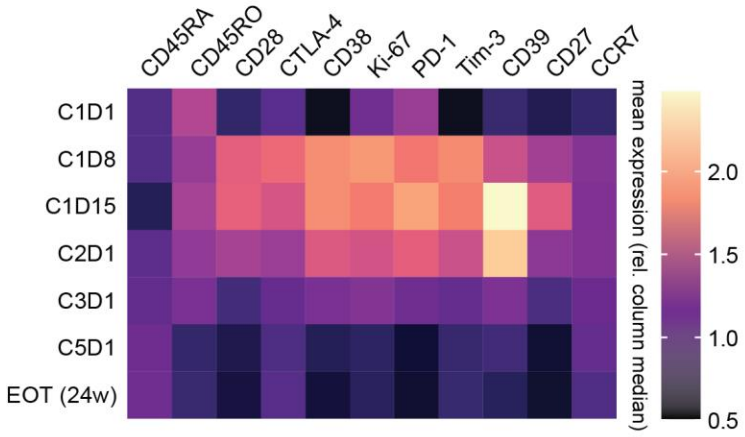


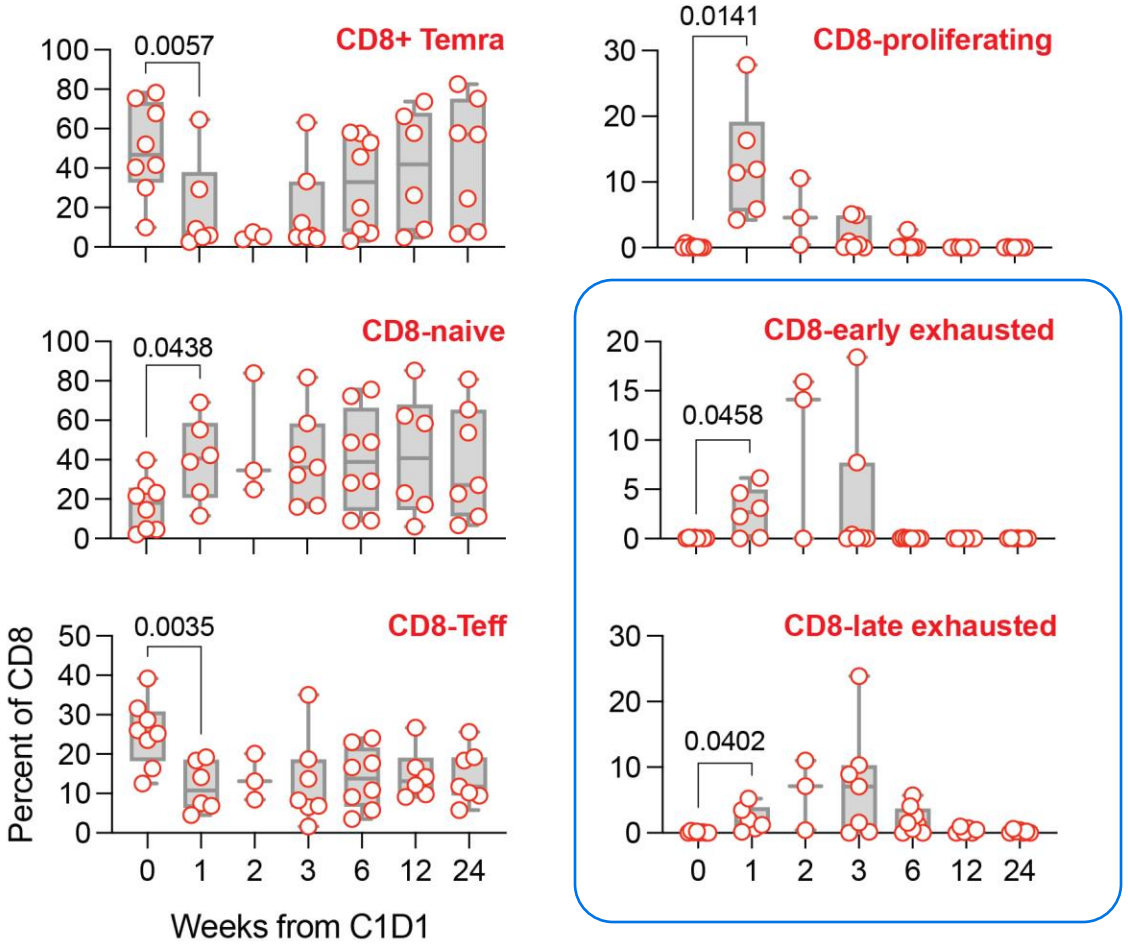


Merryman […] Falchi, ASCO 2023

Insights into SC mosunetuzumab in 1L FL: Hints to mechanisms of resistance





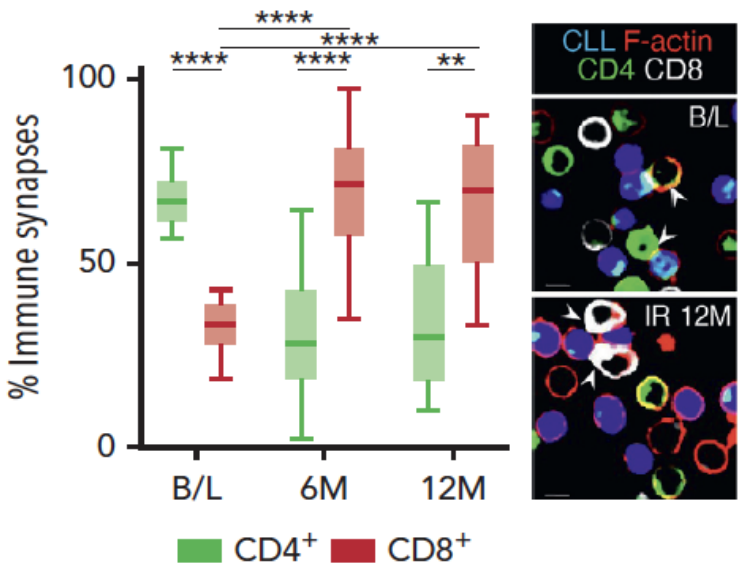


Falchi L et al. ASH 2023. Abstract 604.

BTK inhibitors enhance CD8+ tumor response and may synergize with bispecific antibodies

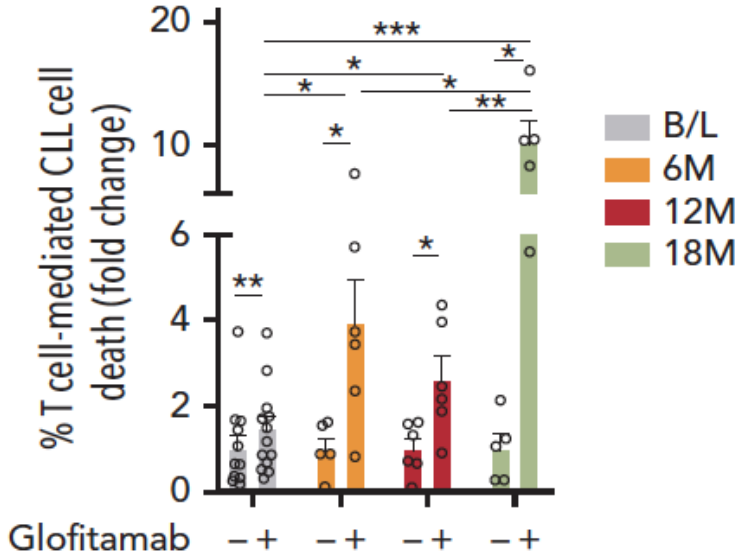
Serial peripheral blood samples from patients treated in study E1912

Ibrutinib + rituximab



- %CD4+ or CD8+ T-cell:CLL conjugates at baseline, 6M, and 12M (n = 15).
- Representative confocal images of CD8+ (white) and CD4+ (green) T-cell conjugates with CLL B cells (blue)

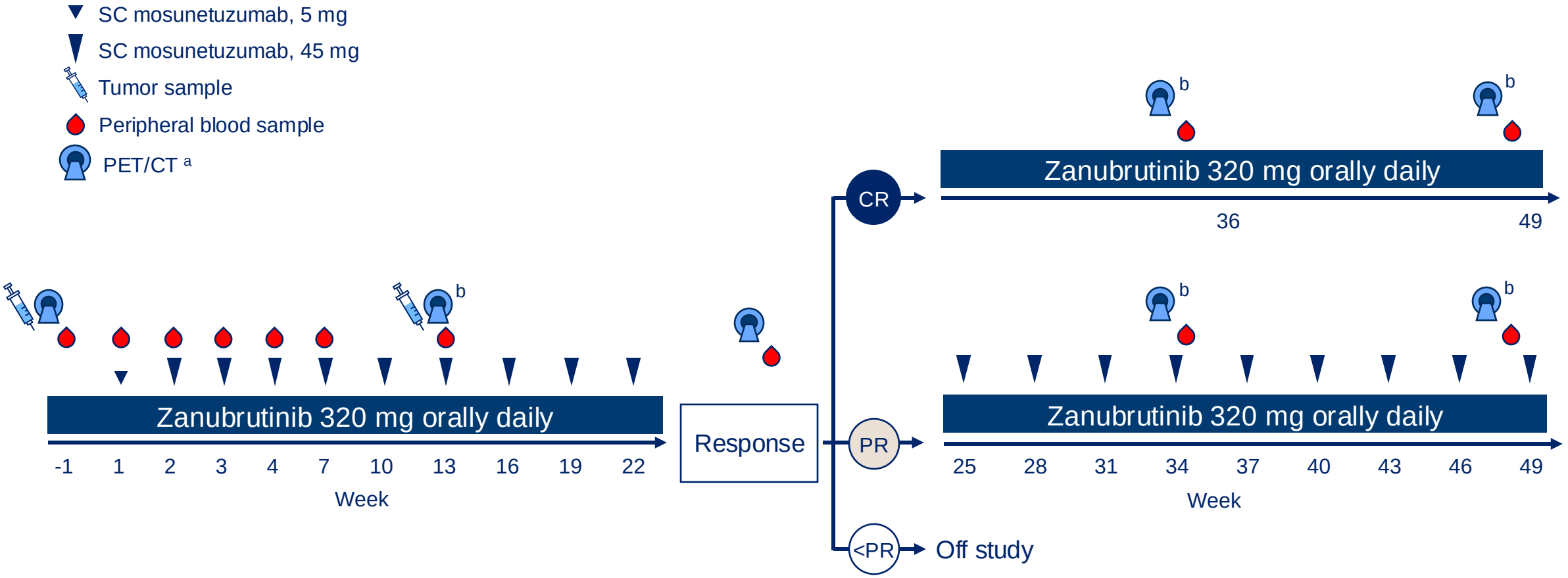
Ibrutinib + glofitamab



- T-cell–mediated CLL cell death using purified T cells from B/L, 6M, 12M, or 18M ibrutinib-rituximab time points against target B/L CLL B cells after ex vivo treatment with glofitamab (0.01 µg/mL) or nonbinding antibody control

Papazoglou et al. Blood . 2024 Jan 4;143(1):57-63

Mosunetuzumab + Zanubrutinib in 1L FL: Study design

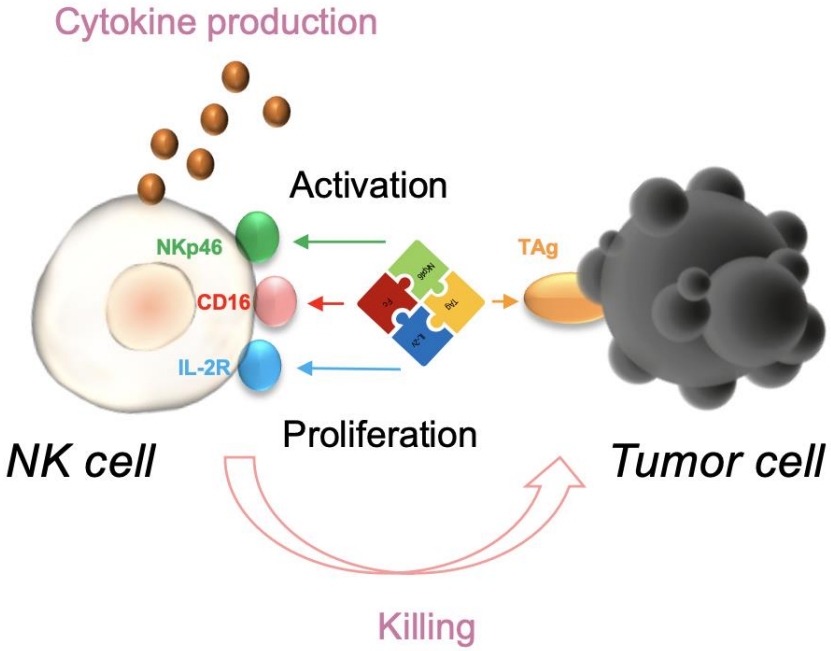


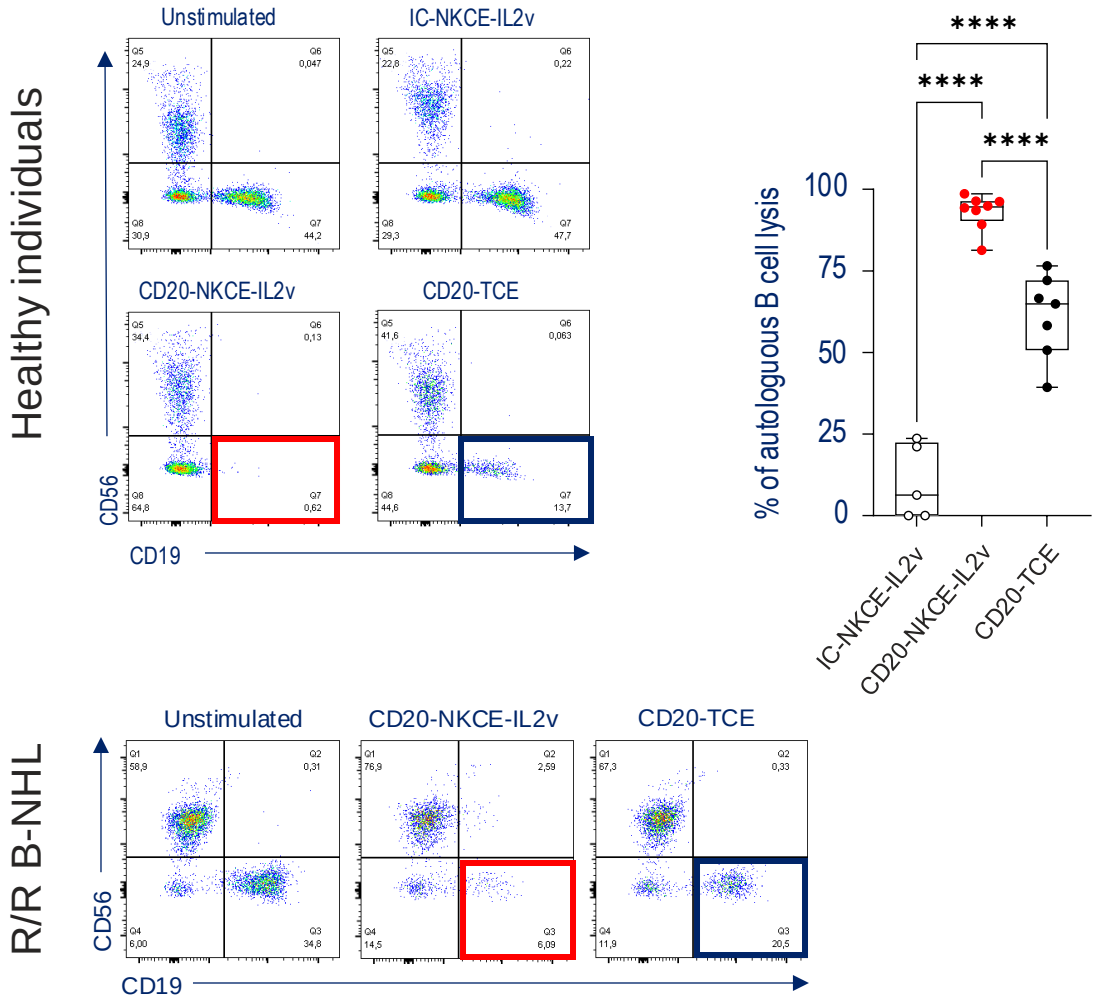
PET/CT, positron emission tomography/ computerized tomography; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; [b] CT must be of diagnostic quality; [a] Patients who experience PD will be taken off study. A biopsy to confirm PD is recommended.

Mechanism of resistance #3

Non-T-cell microenvironmental changes: No data!

IPH6501, first-in-class tetraspecific NK-engager targeting CD20 for the treatment of B-NHL



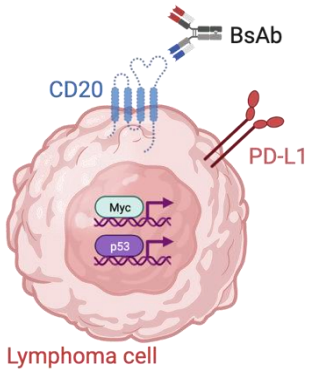


Gauthier L et al. *Cell*. 2019;177(2):1701-1713. Colomar-Carando N et al. *Cancer Immunol Res*. 2022;10(3):291-302. Gauthier L et al. *Nature Biotech*. 2023;41:1296-1306. Demaria O et al. *Cell Rep Med*. 2022;3(10):100783; Demaria O et al. *Science Immunol, in press*.

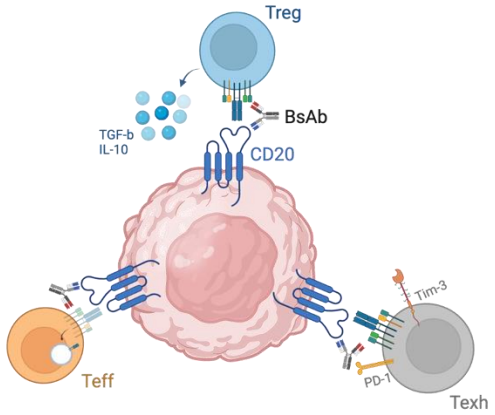
Overcoming resistance to CD20xCD3 bispecific antibodies

Mechanisms of resistance

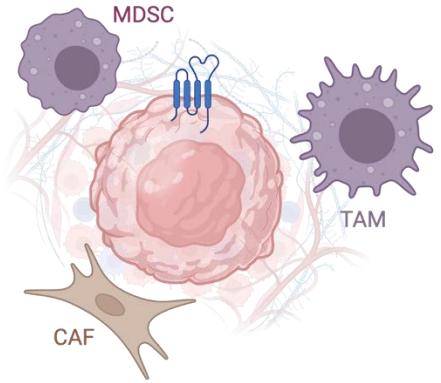
Tumor-intrinsic



T-cell-intrinsic



Tumor- and T-cell-extrinsic



Strategies to overcome resistance

Target different antigens
- BsAb against CD19, CD22, CD79b, ROR1
- Tri- or tetra-specific Ab

Increase T-cell activation / Prevent T-cell exhaustion
- Immunomodulators (e.g. IMiDs)
- Co-stimulatory BsAb

Target the microenvironment
- Lenalidomide; EZH2i; cbl-B-i

Recruit other immune players
- NK cells (IPH6501)
- Macrophages (CD47i)

Modified from Falchi L et al. *Blood*. 2023;141(5):467-480.

Take-home messages and open questions

- **BsAb are a critically important addition in R/R B-NHL**
  - Consistent efficacy with predictable safety
  - The majority of patients experience progression / relapse
- **Resistance to BsAb is multifaceted**
  - CD20 loss is highly prevalent and associated with BsAb failure
  - Many unknowns in T-cell dependent resistance (timing, topography, reversibility)
  - No information on the role of other immune cells
- **Strategies to overcome resistance are emerging**
  - High response rates with emerging combinations
  - Is CD20 reversible in some cases?
  - Should T-cell subsets be differentially leveraged for optimal efficacy (rather than pan-T-cell strategies)?

Acknowledgements

MSK Lymphoma Faculty

Alec Boardman, MD
Philip Caron, MD
Kevin David, MD
Zachary Epstein-Peterson, MD
Paola Ghione, MD, MSEpi
Paul Hamlin, MD
Steev Horwitz, MD
Andrew Intlekofer
William Johnson, DO
Anita Kumar, MD
Jennifer K. Lue, MD
Alison, Moskowitz, MD
Ariela Noy, MD
Colette Owens, MD
M. Lia Palomba, MD
Raphael Steiner, MD
Robert N. Stuver, MD
Pallawi Torka, MD
Andrew Zelenetz, MD
Gilles A. Salles, MD, PhD

Clinical Team

Lauren Wood, MSN, RN, AGCNS, OCN
Anastasia Martinova, BSN, RN
Daniella Saghian, DNP, RN, FNP
Diane Lee, ANP
Genesis Marte, BSN, RN

Study Research Team

Michelle Okwali, MPH
Alex Ferreira, BS
Clare Grieve, MPH
Sherin Uralil, MD
Monifa Douglas, MS
Walter Ramos-Amador, MPH, MS
Kareem McKenzie, AS
Lauren Tarapata, AS
Devona Reese, AS
Alyson Drost, AS
Jasira Bey, AS

Chaya Friedman, MBA, CCRP
Mashiyate Meem, BA
Maria Chabowska, BS

Translational Science Team

Santosha Vardhana, MD, PhD
Jahan Rahman, BS
Lauren Menendez, BS
Ya-Hui (Nicole) Lin, MS

Pallawi Galera, MD
Ahmet Dogan, MD, PhD

Hackensack UMC Team

Lori Leslie, MD
Andre Goy, MD, MS
Gabriella Magarelli, MSN, ACNP, AONCP
Elizabeth McCarty, MSN, RN
Greg Daszkiewicz, CRC
Krupa Patel, CRN
Emilija Camarco, CRN
Sabrina Kdiry, CRN
Danielle Ramirez, CRN

Georgetown Lombardi CCC Team

Joseph Roswarski, MD
Kieron Dunleavy, MD
Thomas White, RN

Funding

LYMPHOMA RESEARCH · FOUNDATION

MSK Steven A. Greenberg Lymphoma Research Award


Memorial Sloan Kettering
Cancer Center