Bispecific Antibodies in B-NHL: BAFF-R

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Disclosures

Consultancy (to institution)	Abbvie, Adaptive, ADC, AstraZeneca, Avencell, BeOne, BMS, Caribou, Genentech/Roche, Janssen, Legend, Lilly/Loxo, Merck, Pfizer, Sanofi
Research Funding (to institution)	Abbvie, AstraZeneca, Avencell, BMS, Genentech/Roche, Janssen, Kite, Lilly/Loxo, Merck, Nurix, Pfizer, Sanofi
Stock	None
Employment	N/A

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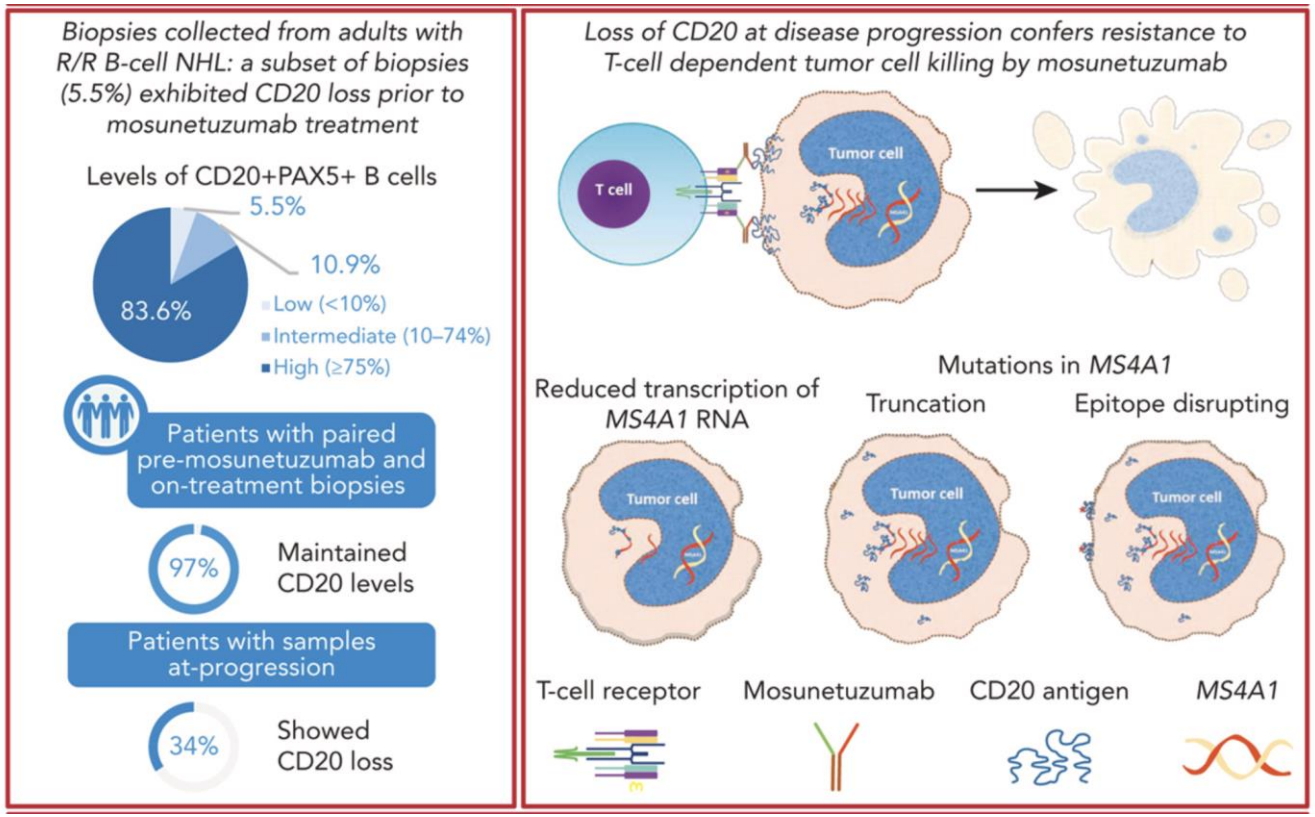
Mechanisms of CD20 BsAb resistance: Antigen Loss

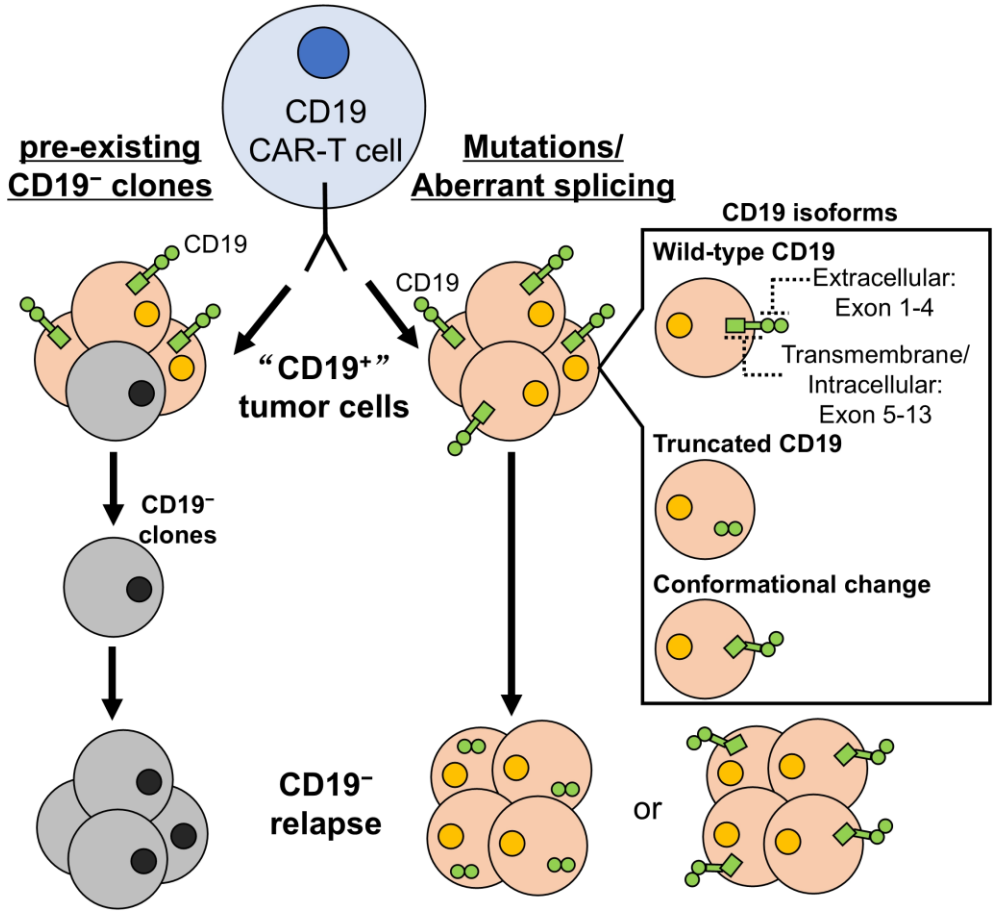


Loss CD20 expression at progression

- Mosun (GO29781 Ph ½) ~ 11 of 32 (34%), mixed iNHL and aNHL
- Glofit (Peter Mac) ~13 of 22 (59%), 3L+ DLBCL
  - Median PFS 2.5 mths (vs 5.5 mths)
  - Median post progression OS 4.4 mths (vs 10.4 mths)

Grigg S et al BJH 2024; Schuster S et al Blood 2024

Mechanisms of CD19 therapy resistance



Loss CD19 expression at progression

- Axi-cel ~ 25-30% at least
  - Median post progression OS 6 mths
- Tisa-cel ~25%

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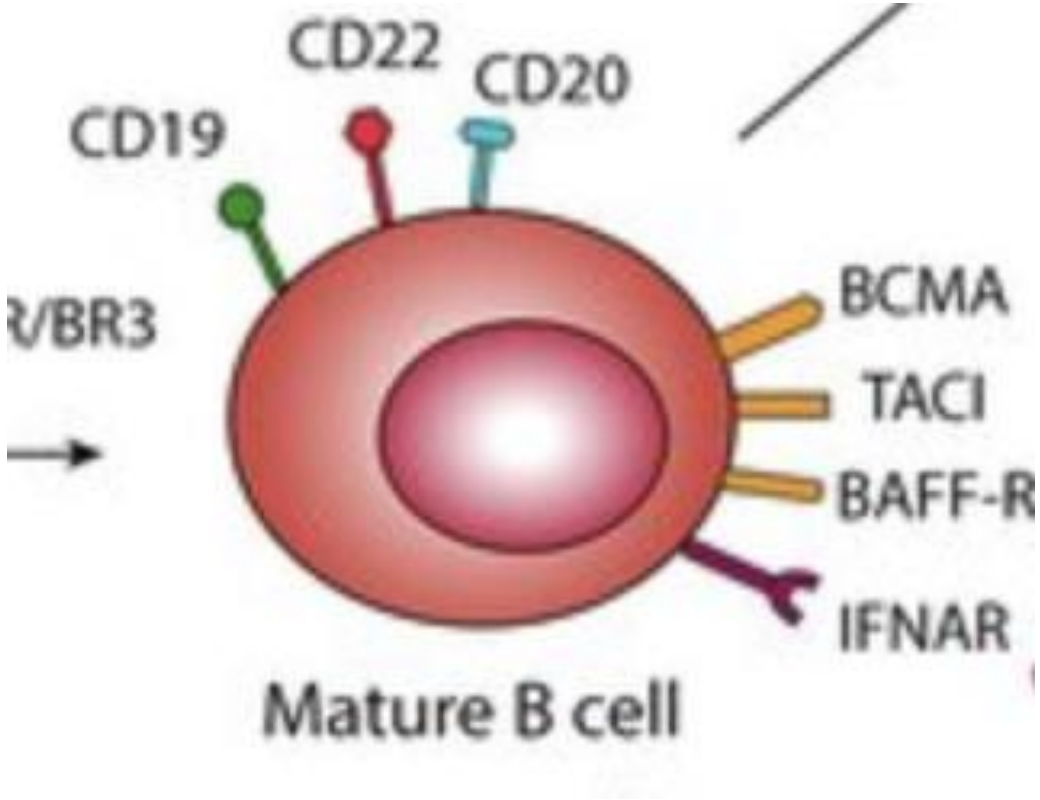
Spiegel J et al Blood 2021; Plaks V et al Blood 2021; Ghilardi G et al Blood 2022

Alternative Targets for BsAb therapies



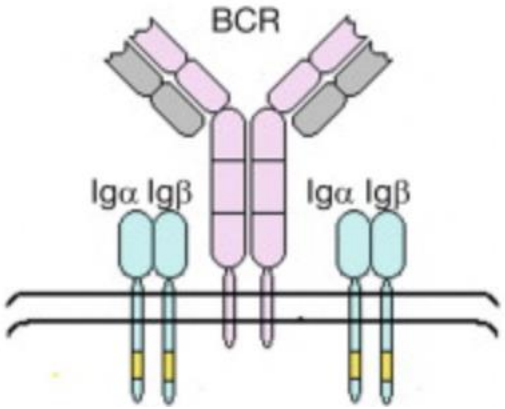
Multiple other cell surface antigens common in B NHL

BAFF-R, CD20, CD22, CD79b

Modified from Blanc, Bousseau et al. 2011; Marta et al. 2017

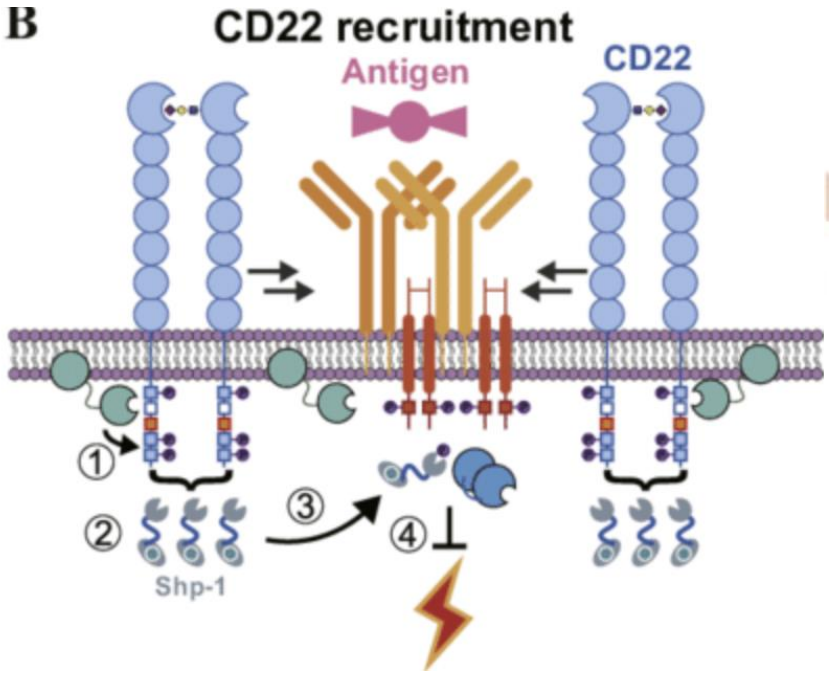
Putative B-cell Cell Surface Targets: Function

CD79B (Igβ)



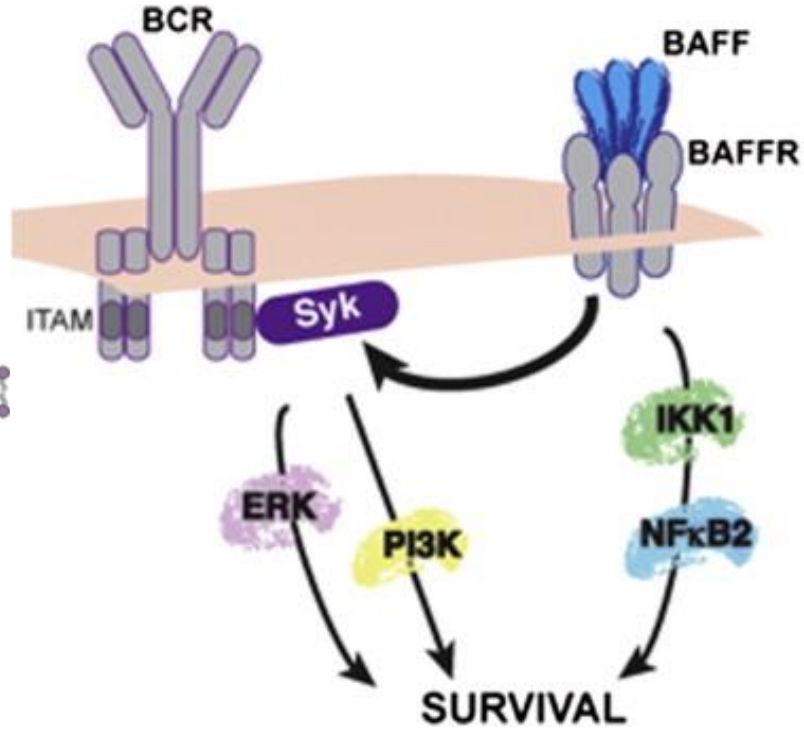
- Survival signaling via NF-kB PI3K and MAPK

CD22



- CD22 activation inhibits BCR signaling

BAFF-R



- Survival signaling via non-canonical NF-kB and Pi3K

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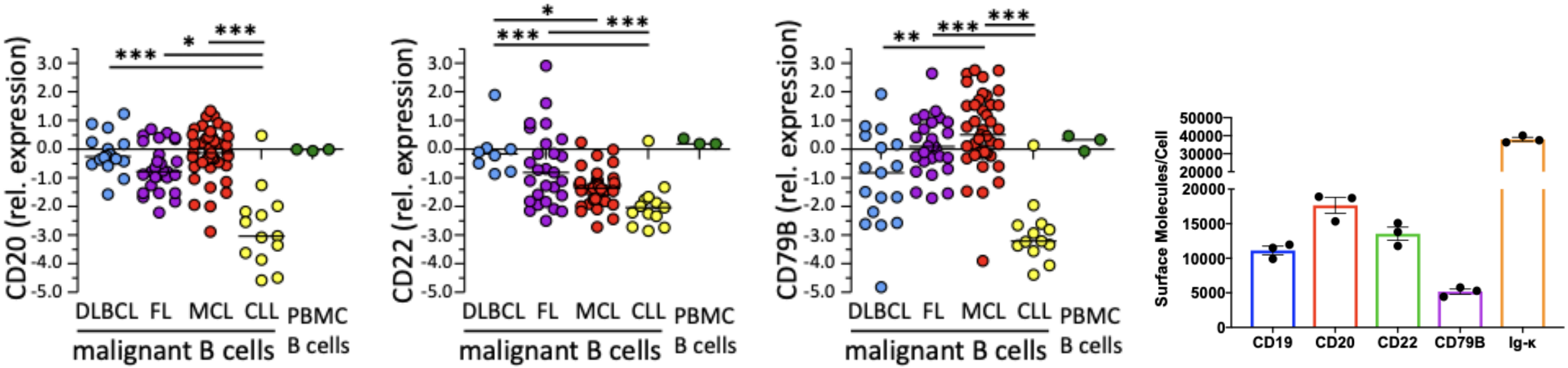
Xu W et al. Blood 2021; Clark E et al Fron Immunology 2018; Schweighoffer, E et al Immunity 2013

Expression of CD22 and CD79B in B-NHL

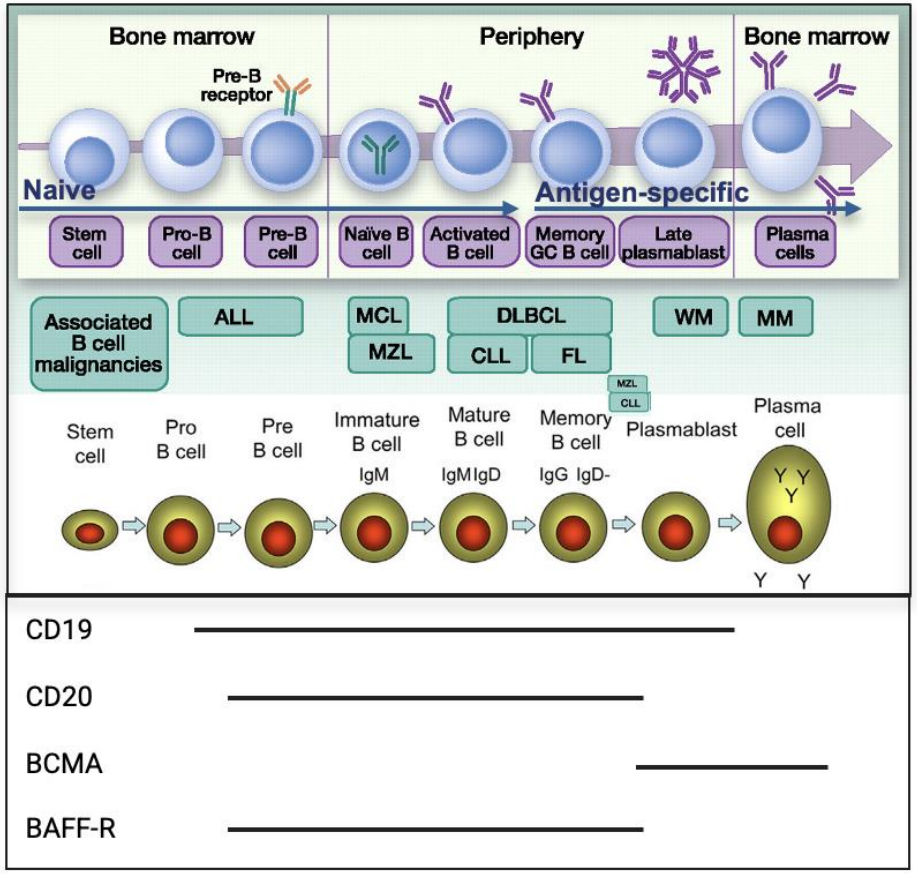


CD22, CD79B expression varies across B-cell NHL histologies (relative to normal mature B-cells)

Surface density of B-cell markers may also vary

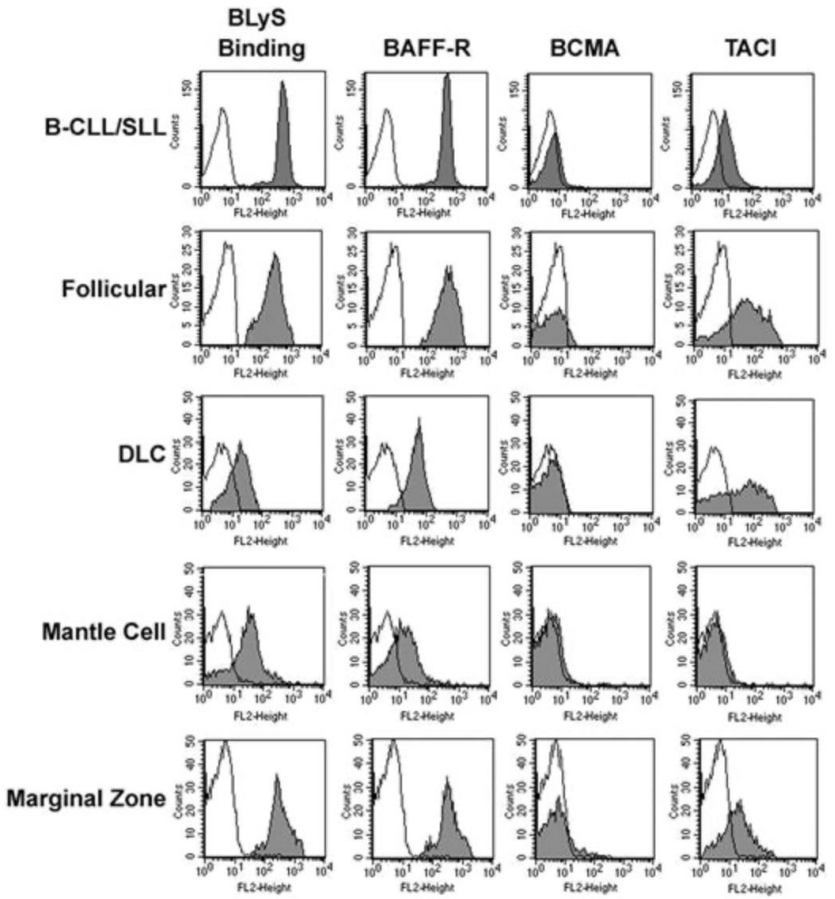
Majzner R et al. Cancer Discovery 2020

Expression of BAFF-R in B-NHL



Modified from Blanc, Bousseau et al. 2011; Marta et al. 2017

Near universally expressed

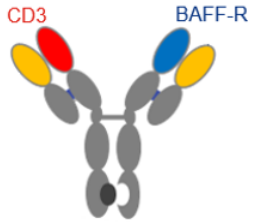


Novack R et al Blood 2004; Blanc, et al 2011; Marta, et al 2017

BAFF-R x CD3: LY4152199

Table 1: Binding characteristics of LY4152199

Binding Arm	Affinity at 37°C (nM)	Cross Reactivity
BAFF-R	0.42	Cyno
CD3	CD3εδ: 28.7	N/A
	CD3εγ: 50.9	

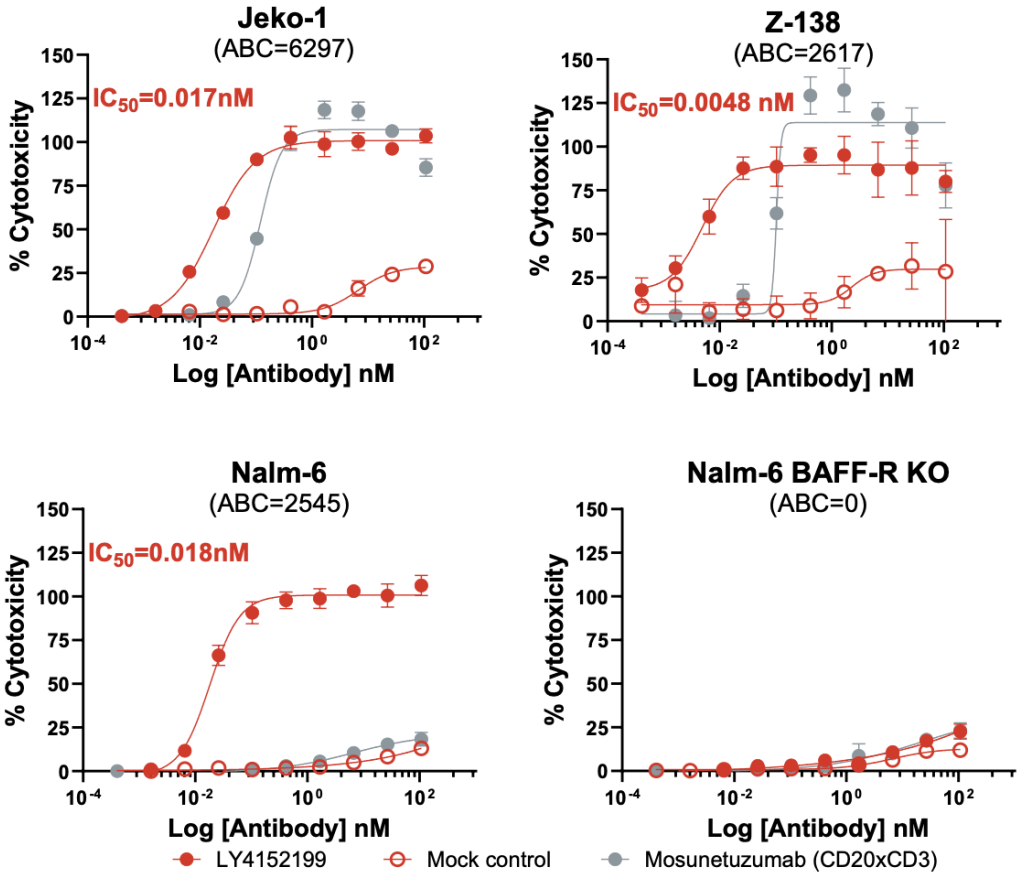


Full humanized Fc silenced

LY4152199→ significant cytotoxicity at low nM concentrations (lower than mosun)

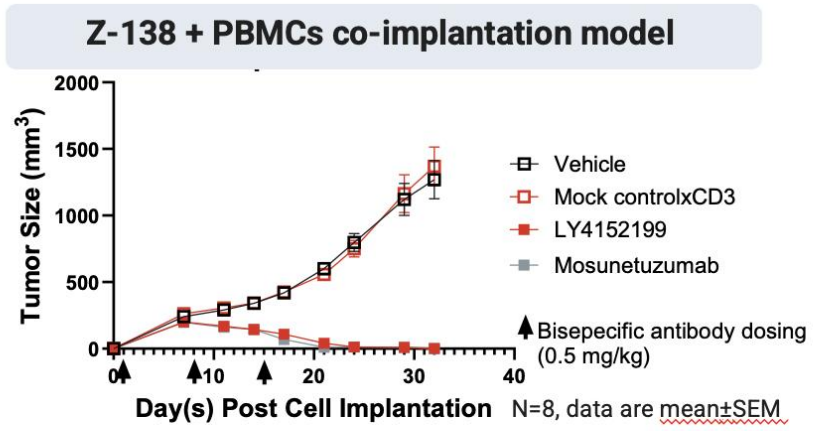
BAFF-R specific cytotoxicity in vivo
Effective in low CD20 NALM6 model

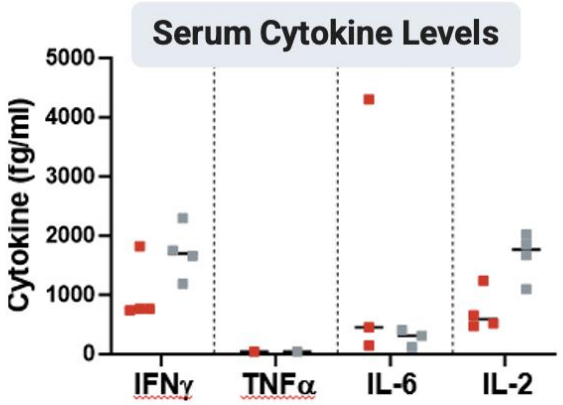
Fig 2. LY4152199 demonstrates target-dependent tumor cell killing including cells with minimal CD20

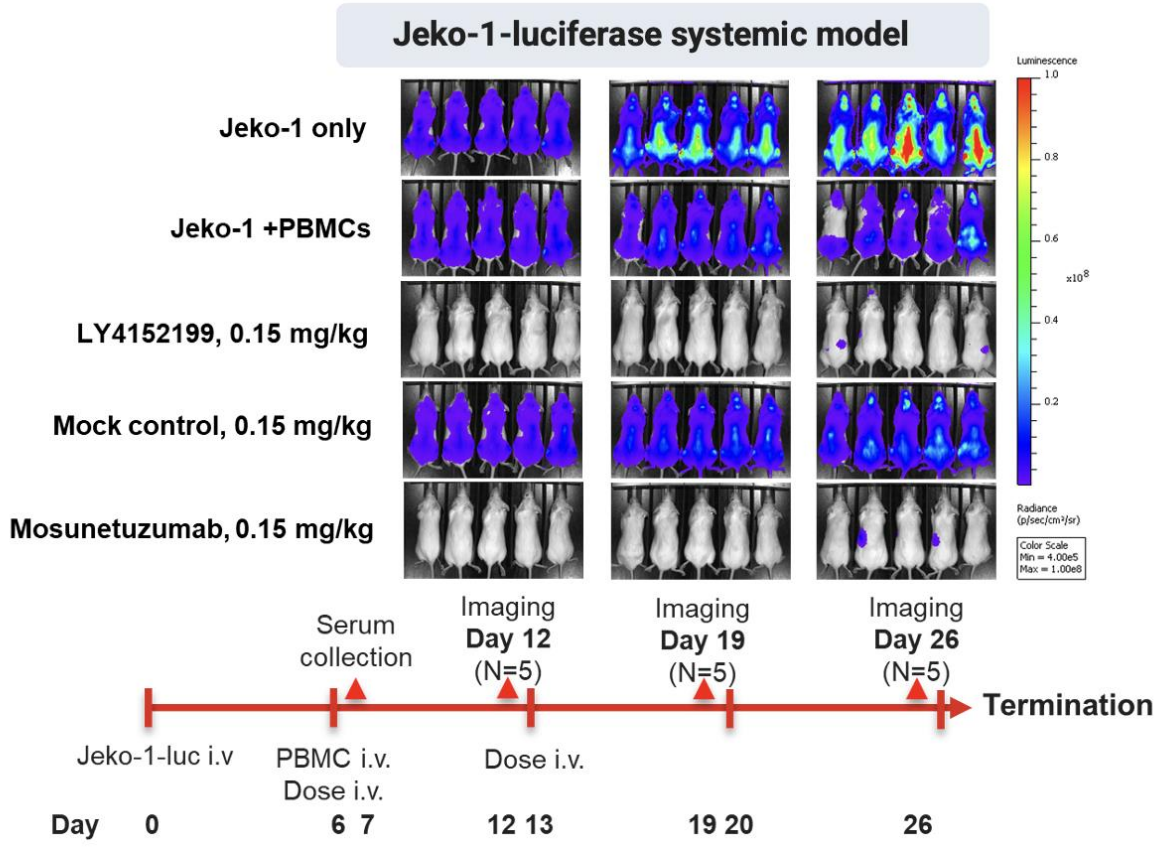


Yang W et al ASH 2024

BAFF-R x CD3: LY4152199







Significant activity in Z-138 and Jeko Xenograft models
Lower serum cytokine induction in mouse models

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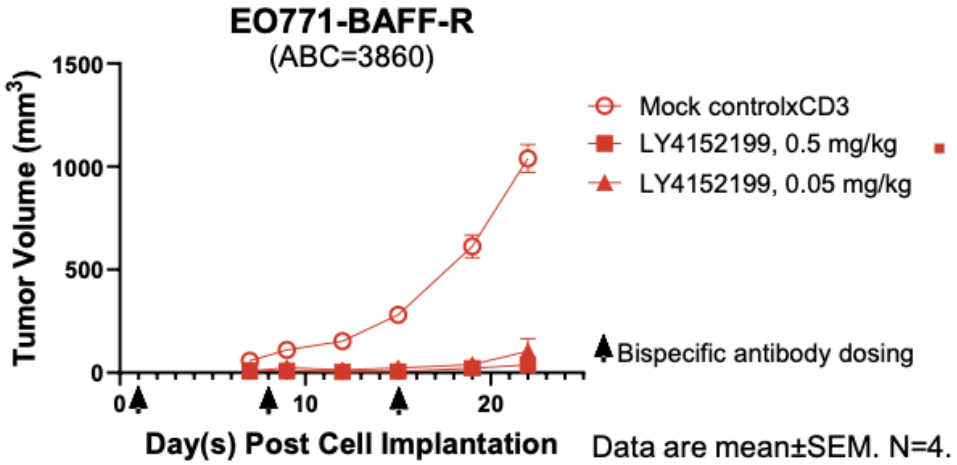
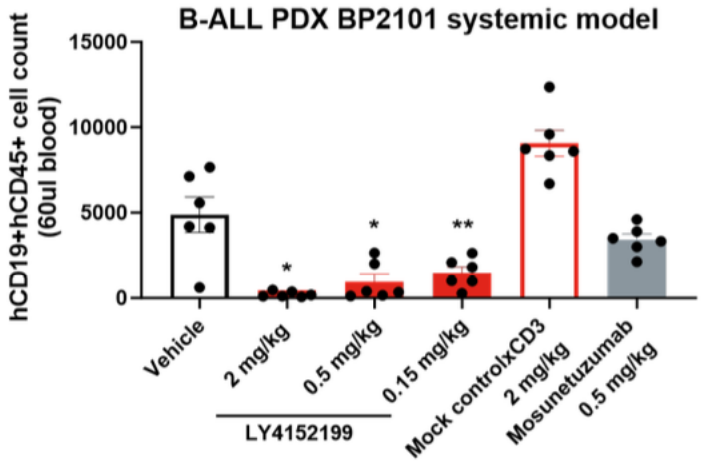
BAFF-R x CD3: LY4152199



- LY4152199 shows potent anti-tumor activity against human BAFF-R-expressing syngeneic mouse tumor model in humanized CD3EDG mice with competent immune system, at dose as low as 0.05 mg/kg

Potent anti-tumor activity at low doses

Dose dependent B-cell depletion



- LY4152199 reduces B cells in patient derived B-ALL model humanized with PBMCs in a dose-dependent fashion 24hr after 3rd bispecific antibody dosing
- LY4152199 completely depletes patient derived B-ALL B cells at 2 mg/kg

- Patient derived B-ALL model BP2101 is homogenously double positive for CD19 and BAFF-R. About 30% BP2101 cells are CD20 positive and concomitantly positive for CD19 and BAFF-R. Peripheral blood was collected 24hr after 3rd bispecific antibody dosing for flow analysis of CD19+ cell number.
- One-way ANOVA is used for statistical analysis. Compared to Vehicle *P<0.0001; **P=0.0003.
- Data are mean±SEM

Yang W et al ASH 2024

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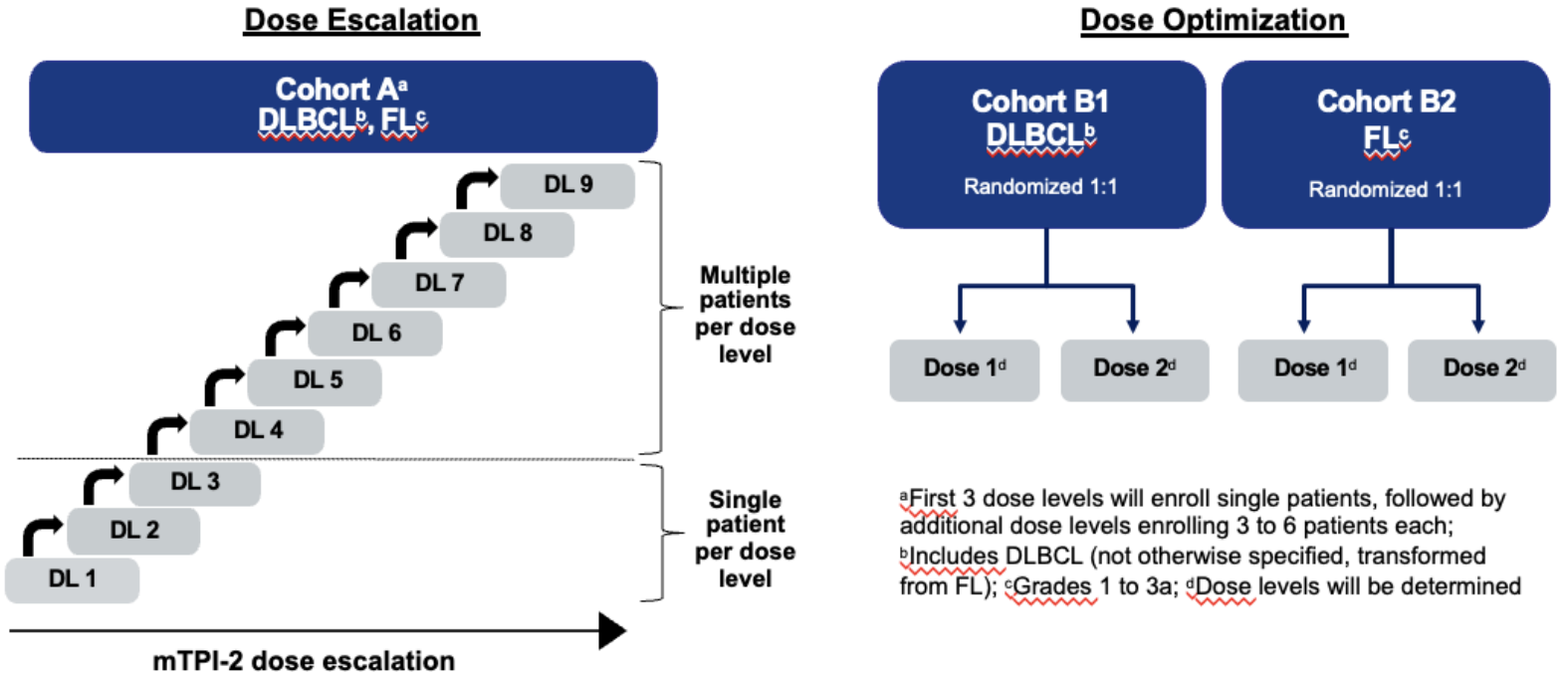
BAF_FRontier-1: Phase 1 LY4152199



Primary

- OBD/RP2D determination of LY4152199 in patients with previously treated DLBCL and FL

Secondary

- Assess the safety and tolerability
- Characterize PK profile
- Assess preliminary efficacy

- LY4152199 will be administered intravenously
- At least two dose levels will be explored in the randomized dose optimization for each disease histology
- Step-up dosing is required for the first cycle at each dose level
- Retreatment will be allowed for patients who have experienced remission for at least 6 months

Future Questions and Directions

Let’s assume varying B-cell antigen’s is safe and efficacious..

Will BAFF-R targeting be superior to CD20 x CD3 BsAb?

-What trial design as CD20 BsAb continue to advance into 1L?

-How will we know best sequence?

What will be the best combination strategy?

-Multiple CD3 x B-cell antigen BsAb?

-Combinations of CD3 and co-stim BsAb?

-Best non BsAb partners?

Can these agents challenge CART?

-Will this be safety, efficacy, both?

-What about BAFF-R targeting CARTs?

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Thank you.

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