Eppur si muove...

La terapia nel MONDO LINFOMI

Il CD19 come target terapeutico nel DLBCL

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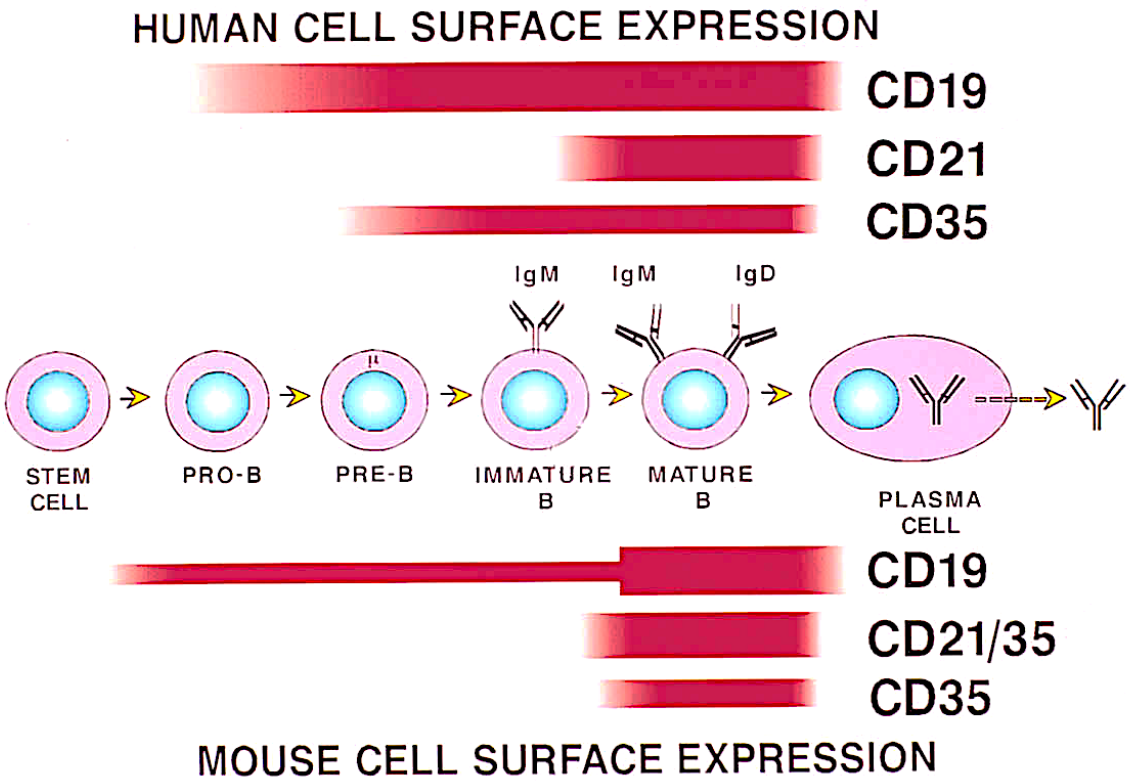
Università di Pisa

BOLOGNA, 8 MARZO 2022

Characteristics of an ideal target

- Stable expression on target cells
- Higher, deregulated expression in malignant cells vs. normal tissues
- Crucial role in malignant cell biology

Expression of CD19, CD21, and CD35 during B cell development in humans and mice



Tedder TF et al. Immunity, 1997;6:107–118

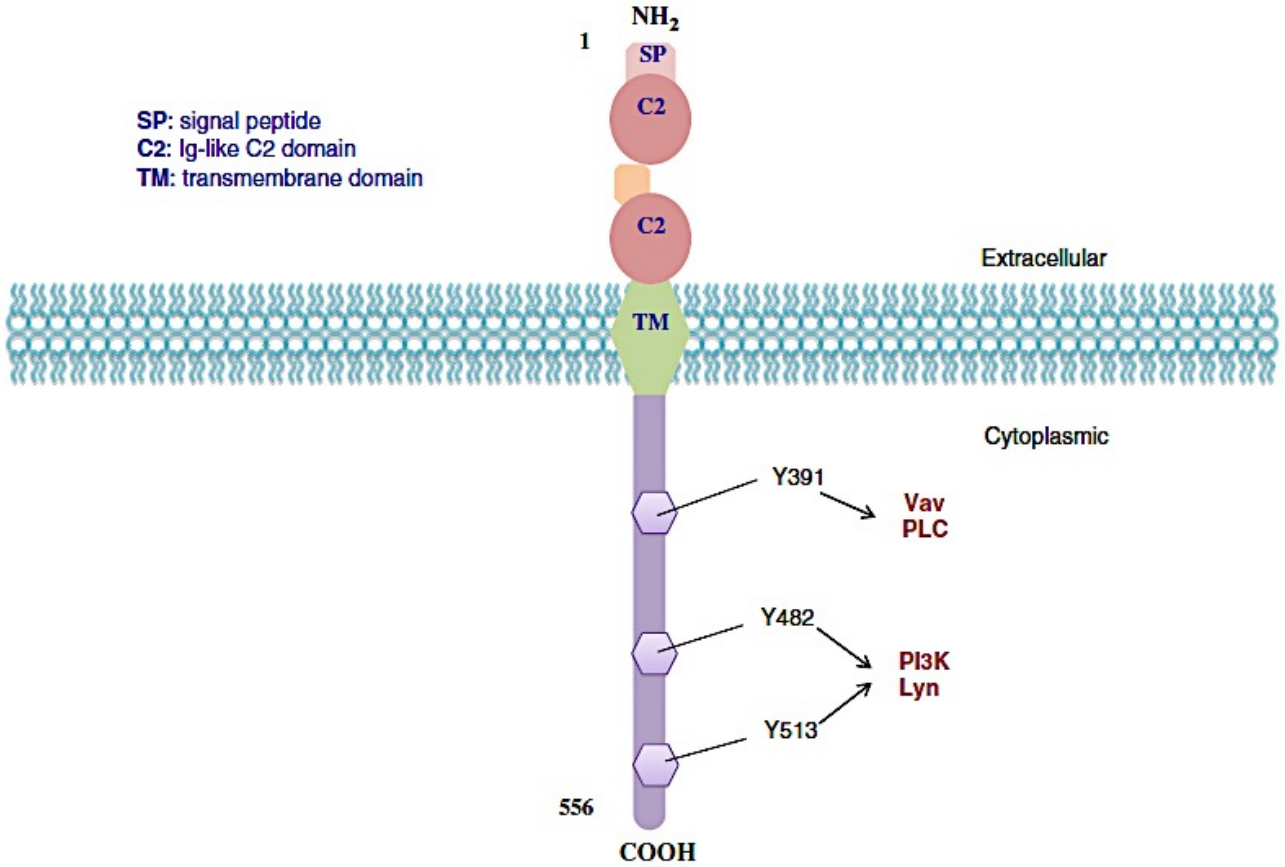
Expression levels of CD19 and CD22 on cell lines

	CD19		CD22	
	MFI*	Sites/cell	MFI	Sites/cell
BL74	720	236,000	68	26,000
CA46	1,085	354,000	280	94,000
DOHH2	734	241,000	130	46,000
KEMI	640	210,000	90	33,000
Raji	1,780	578,000	180	62,000
Ramos	676	222,000	98	35,000

*Median fluorescence intensity (MFI)

Du X et al. Cancer Res. 2008;68:6300-6305

CD19 molecular structure



Wang et al. Experimental Hematology & Oncology 2012, 1:36

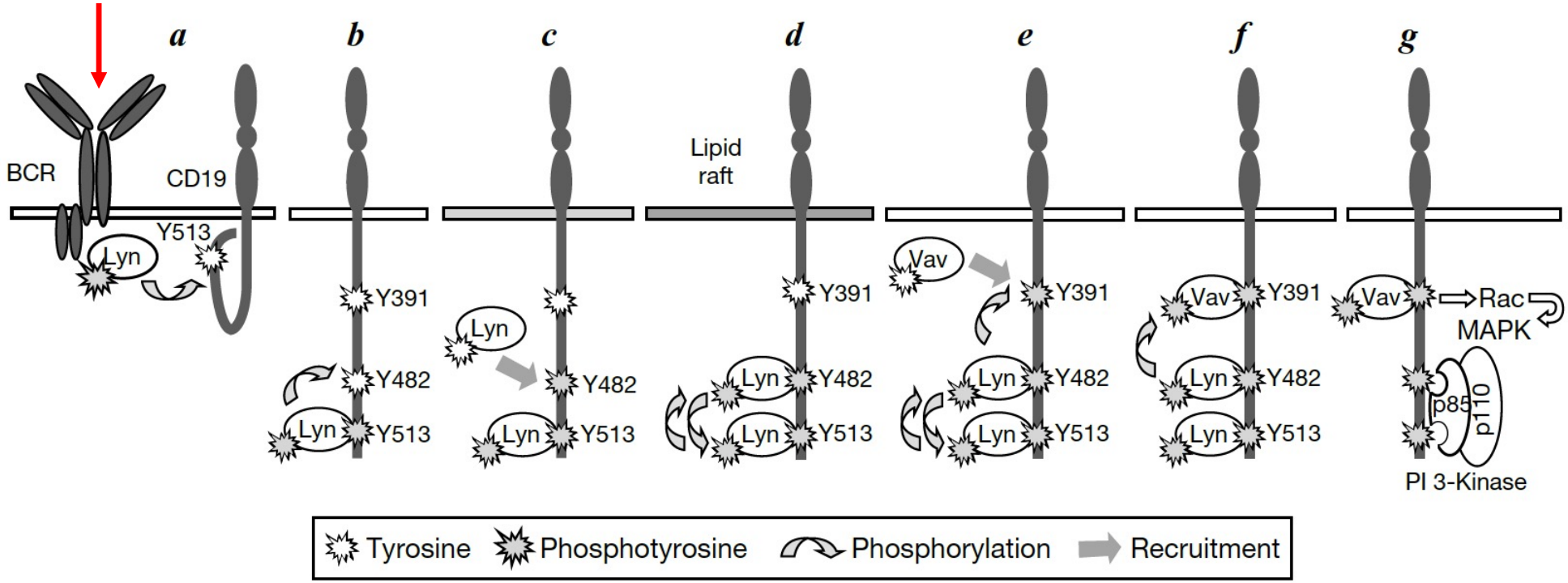
CD19 molecular structure

- The human CD19 antigen is a 95 kd transmembrane glycoprotein belonging to the immunoglobulin (Ig) superfamily
- CD19 is classified as a type I transmembrane protein, with a single transmembrane domain, a cytoplasmic C-terminus, and extracellular N-terminus.
- The extracellular element contains two C2-type Ig-like domains divided by a smaller potential disulfide linked non-Ig-like domain, as well as N-linked carbohydrate addition sites.
- The biologic functions of CD19 are dependent on three cytoplasmic tyrosine residues – Y391, Y482 and Y513.

Wang et al. Experimental Hematology & Oncology 2012, 1:36

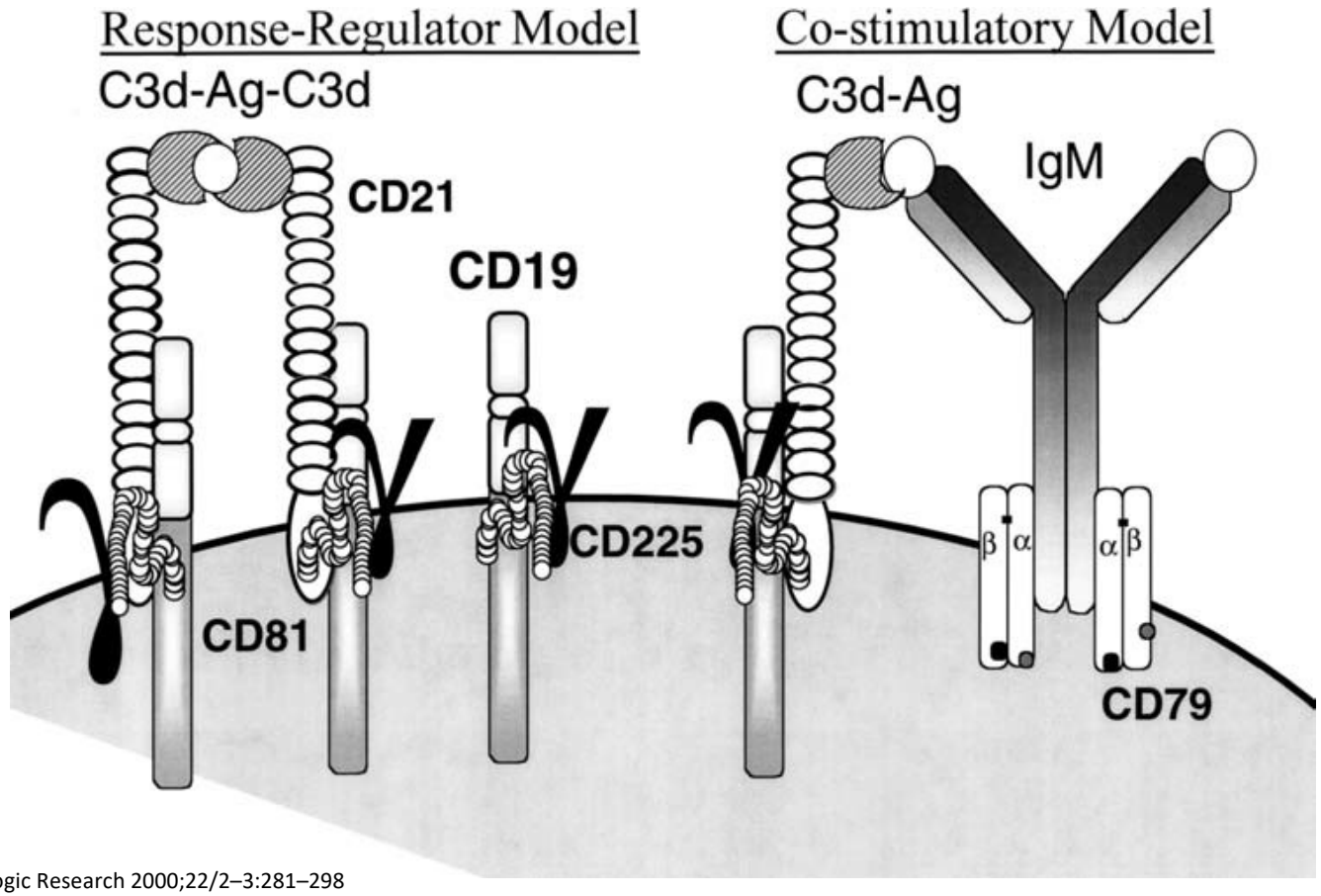
CD19 associated signaling complex

Stimulation



Tedder TF et al. in Stohl W (ed): B Cell Trophic Factors and B Cell Antagonism in Autoimmune Disease. Curr Dir Autoimmun. Basel, Karger, 2005, vol 8, pp 55–90

Models for CD19 function in vivo



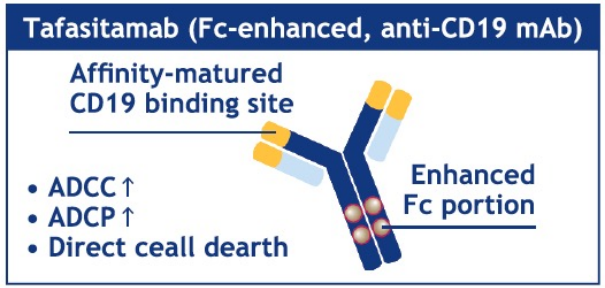
Fujimoto M et al. Immunologic Research 2000;22/2–3:281–298

CD19 disease association

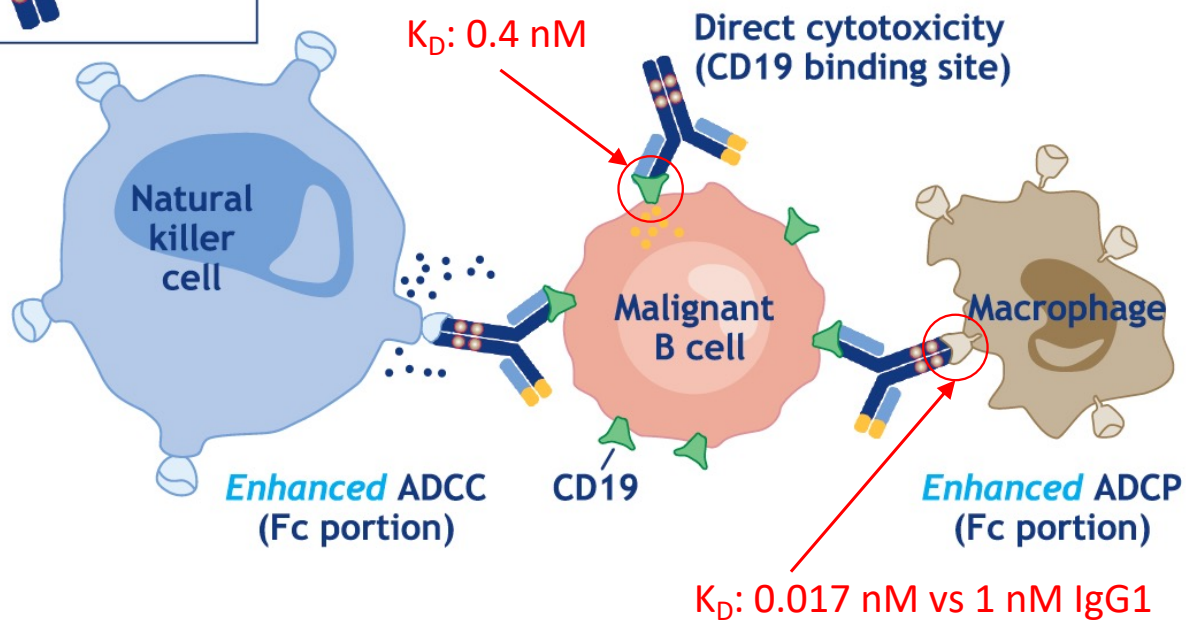
- CD19 expression is highly conserved on most B cell tumors.
- The majority of B cell malignancies express CD19 at normal to high levels (80% of ALL, 88% of B cell lymphomas and 100% of B cell leukemias).
- Recent studies have constructed one model of lymphomagenesis involving CD19 and the proto-oncogene c-Myc.
- A positive feedback pathway in which upregulated CD19 expression and phosphorylation, induced by constitutive c-Myc overexpression, serve to further promote and stabilize c-Myc signaling, whose downstream effectors include important cell cycle regulators like cyclin D2.
- Dysregulation in these regulators subsequently enhance lymphomagenesis.

Wang et al. Experimental Hematology & Oncology 2012, 1:36

Mode of action of tafasitamab



KD and affinity are inversely related. A high affinity interaction is characterized by a low KD



Zalevsky J et al. Blood. 2009;113:3735-3743
Salles G et al. Expert Opinion Biol Ther 2021;21:455-463

Synergistic effect of tafasitamab and lenalidomide

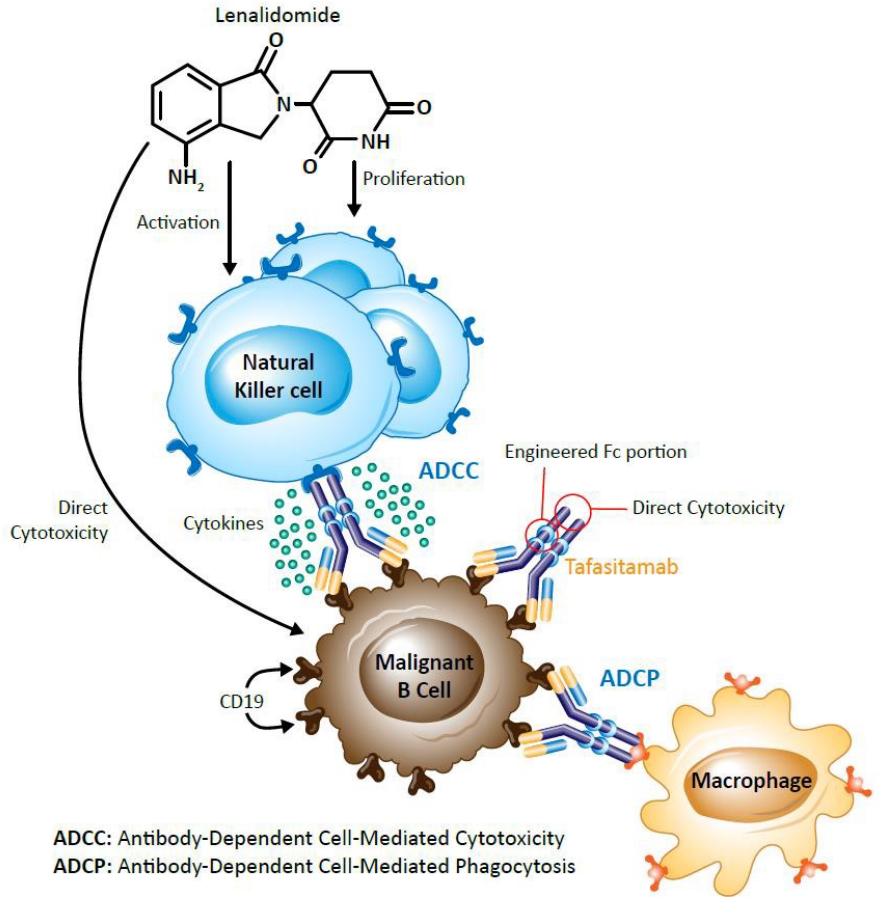
Tafasitamab MoA

- Antibody Dependent Cellular Cytotoxicity via NK cells (ADCC)
- Antibody Dependent Cellular Phagocytosis (ADCP)
- Direct cytotoxicity

Lenalidomide MoA

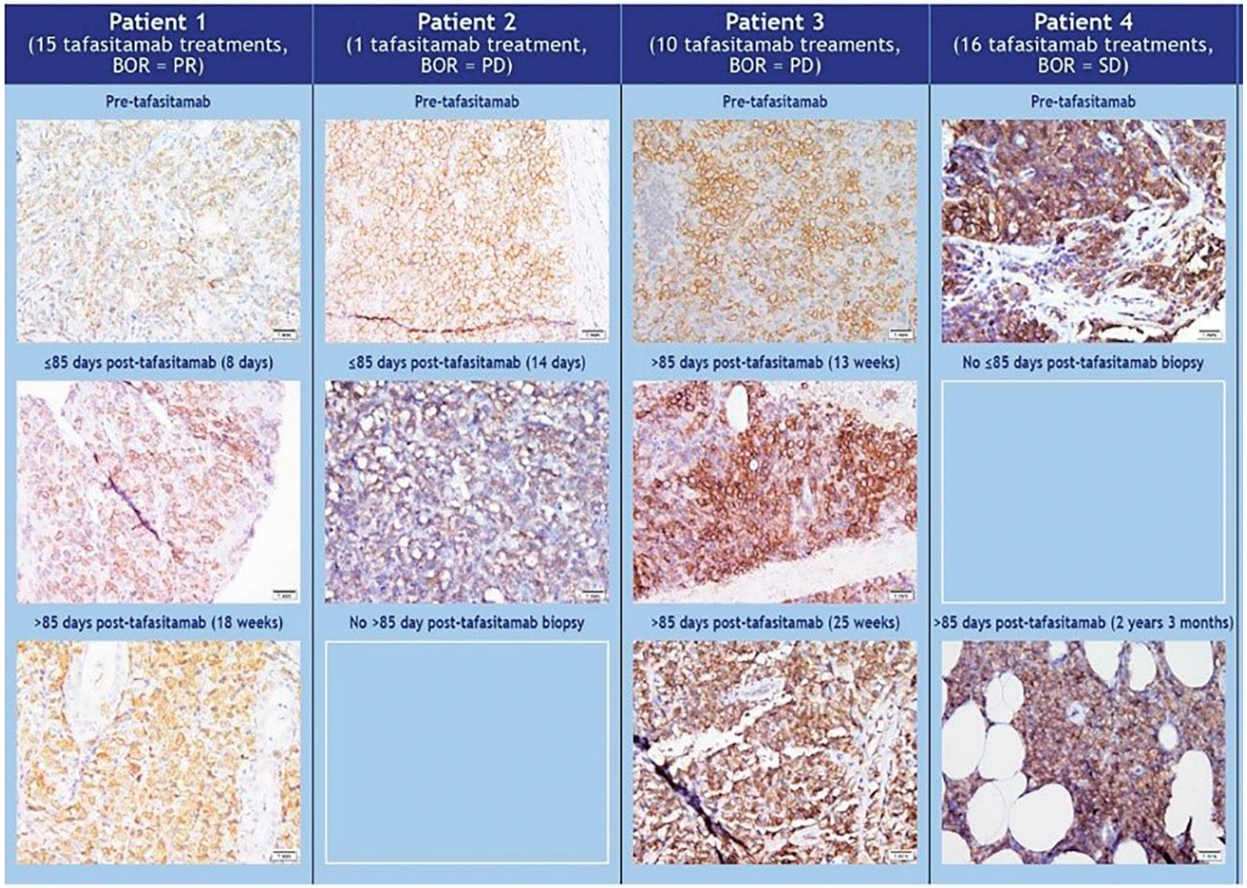
- Direct cytotoxicity
- Increase NK cell numbers (ADCC)
- Activate NK cells

Increased anti-tumor effects



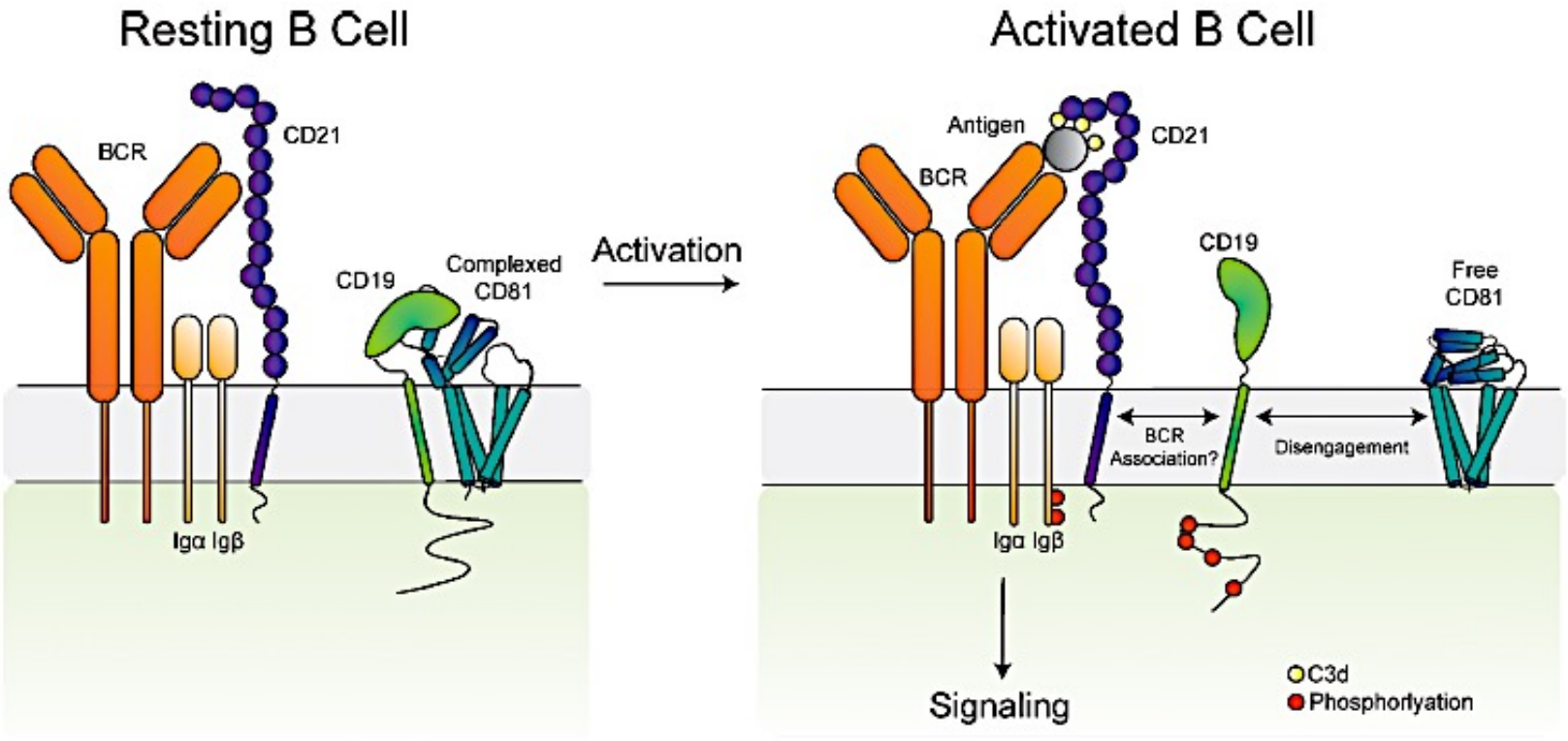
Cheson BD et al. Blood Cancer J 11, 68 (2021)

CD19 expression is maintained in DLBCL patients after treatment with tafasitamab plus lenalidomide



Duell J et al. Leuk Lymphoma 2022;63(2):468-472

Maintenance of CD19 expression is expected as CD19 is part of a multimeric complex



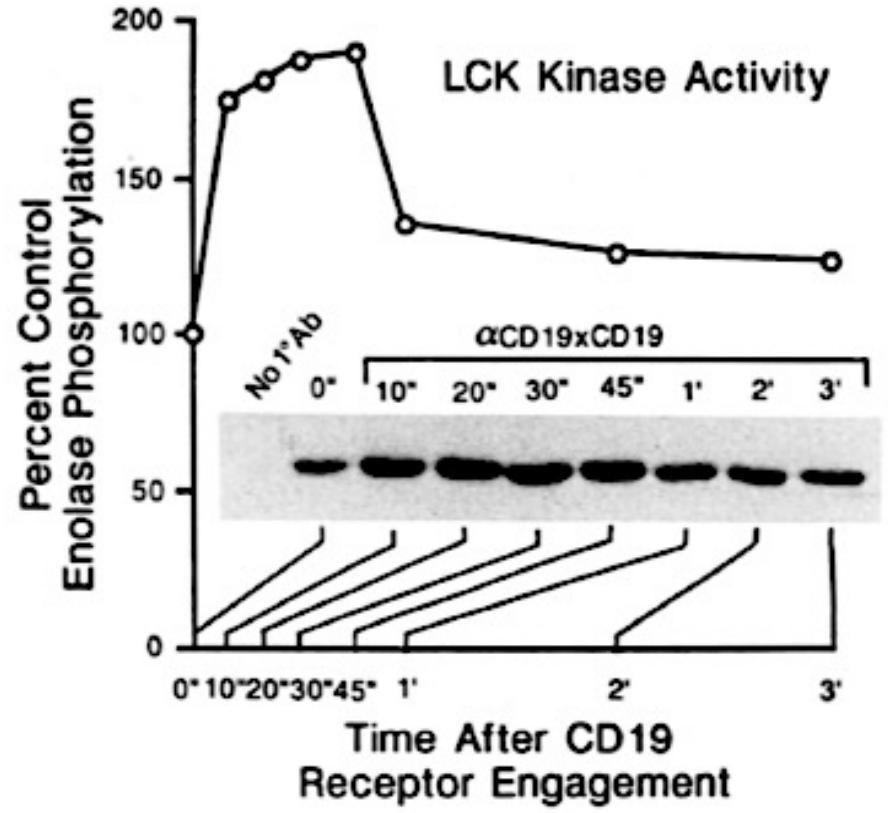
Susa et al. eLife 2020;9:e52337

CD19 expression is maintained in DLBCL patients after treatment with tafasitamab plus lenalidomide

- IHC analysis showed a comparable, distinct CD19 expression before and after tafasitamab therapy in a subset of L-MIND study patients.
- DNA and RNA analyses did not find evidence for CD19 mutations, dominant exon skipping or loss of CD19 mRNA expression, which would be indicative of resistance to further CD19-targeted therapy.
- These findings indicate a maintained CD19 expression after tafasitamab therapy and may provide a rationale for subsequent CD19-directed therapies in patients with R/R DLBCL.

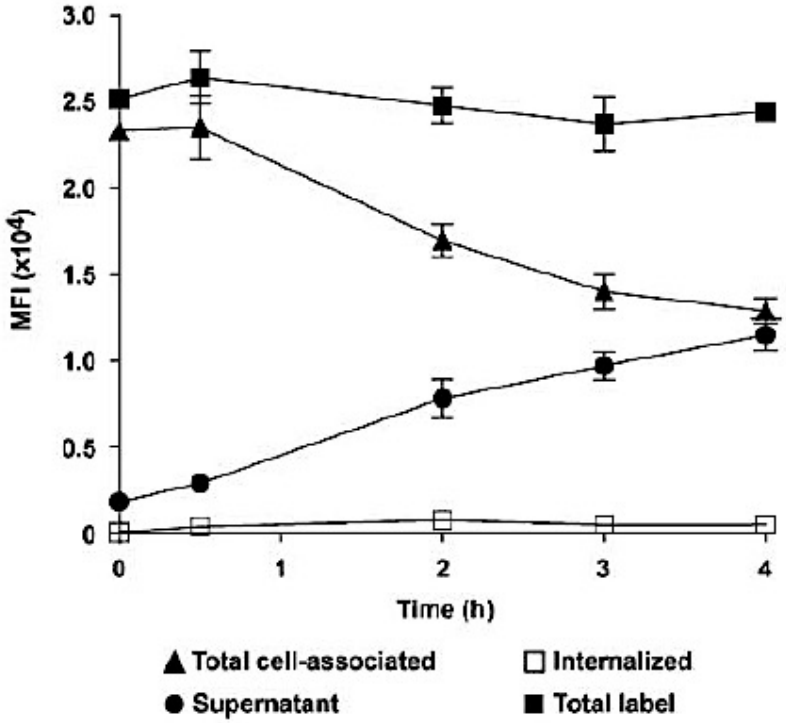
Duell J et al. Leuk Lymphoma 2022;63(2):468-472

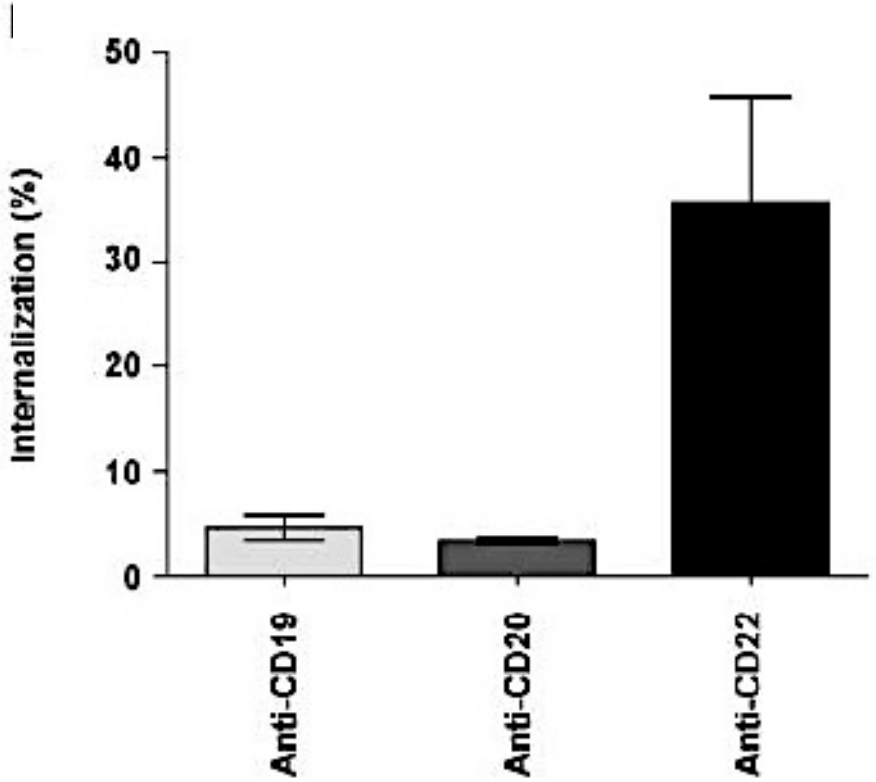
Time course of Src family PTK activation after cross-linking of CD19 receptor molecules with an anti-CD19xCD19 homoconjugate



Uckun FM et al. J Biol Chem 1993;268(28):21172-84

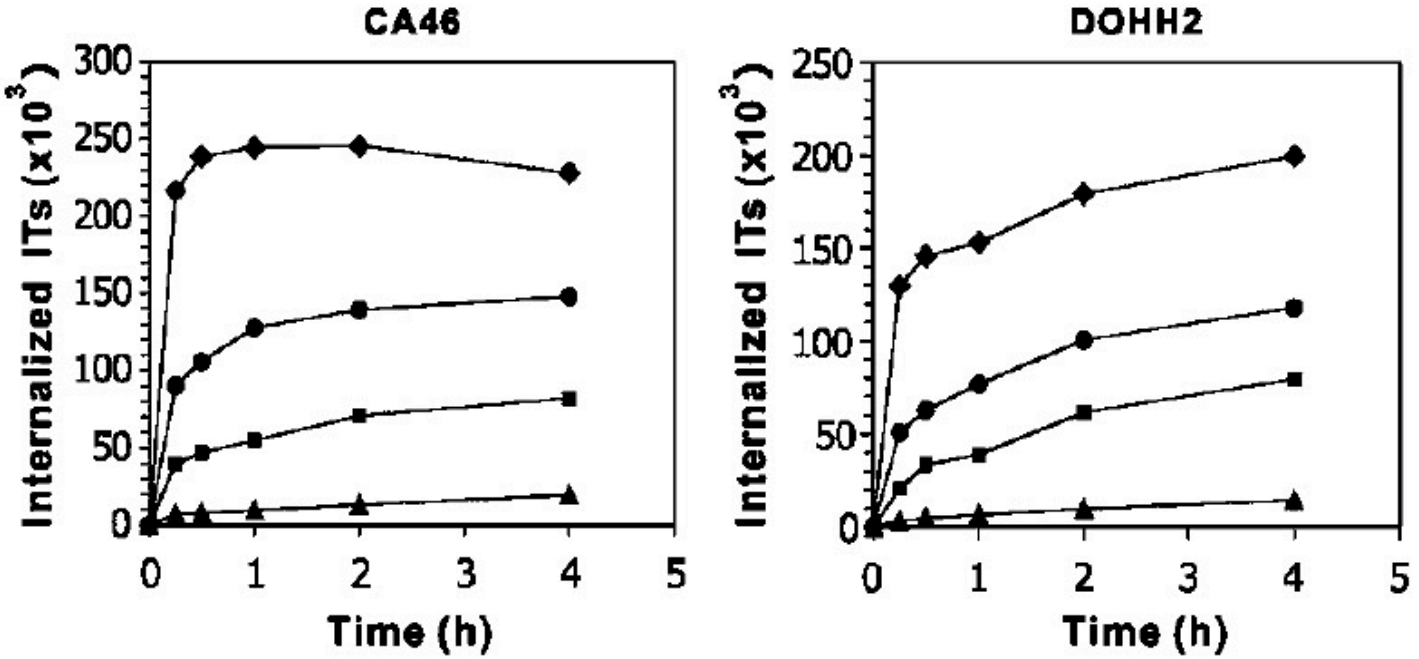
Tafasitamab induces minimal receptor internalization





Horton HM et al. Cancer Res. 2008 Oct 1;68(19):8049-57

Time course of immunotoxin internalization



◆, 100 nmol/L BL22; ●, 10 nmol/L BL22; ■, 100 nmol/L FMC63(Fv)-PE38; ▲, 10 nmol/L FMC63(Fv)-PE38.

BL22: anti-CD22
PE38: anti-CD19

Du X et al. Cancer Res. 2008;68:6300-6305

Masking or simply a mechanism of resistance to treatment?

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2021.1992622

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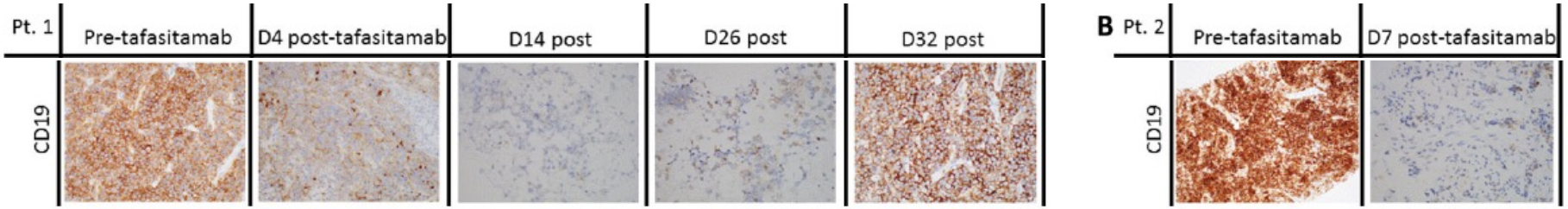
LETTER TO THE EDITOR

CD19 epitope masking by tafasitamab leads to delays in subsequent use of CD19 CAR T-cell therapy in two patients with aggressive mature B-cell lymphomas

Kelly N. Fitzgerald[a], Andres E. Quesada[b], Gottfried von Keudell[a], Sandeep Raj[a], Natasha E. Lewis[b], Ahmet Dogan[c], Gilles Salles[a] and M. Lia Palomba[a]



Conclusions

- CD19 is an important target of therapeutic intervention
- Its involvement in signal transduction pathways of pathologic B-cells is well documented.
- CD19 is highly expressed on cell membrane
- Antibody effector function could be affected by internalization of the antibody-antigen complex.
- Very little internalization and target vanishing occurs after tafasitamab administration.