Eppur si muove...

La terapia nel MONDO LINFOMI

Il CD19 come target terapeutico nel DLBCL

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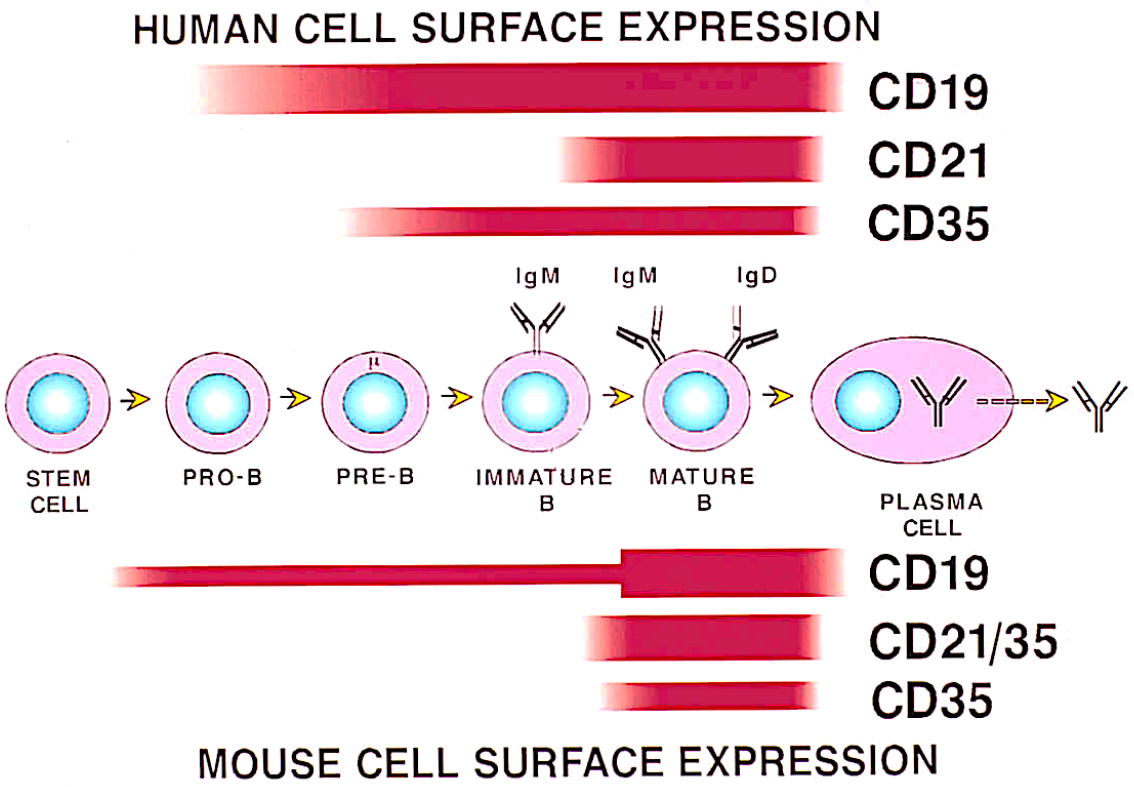
Disclosures

- *Consultant*
  - *Ipsen*
  - *Novartis*

Characteristics of an ideal target

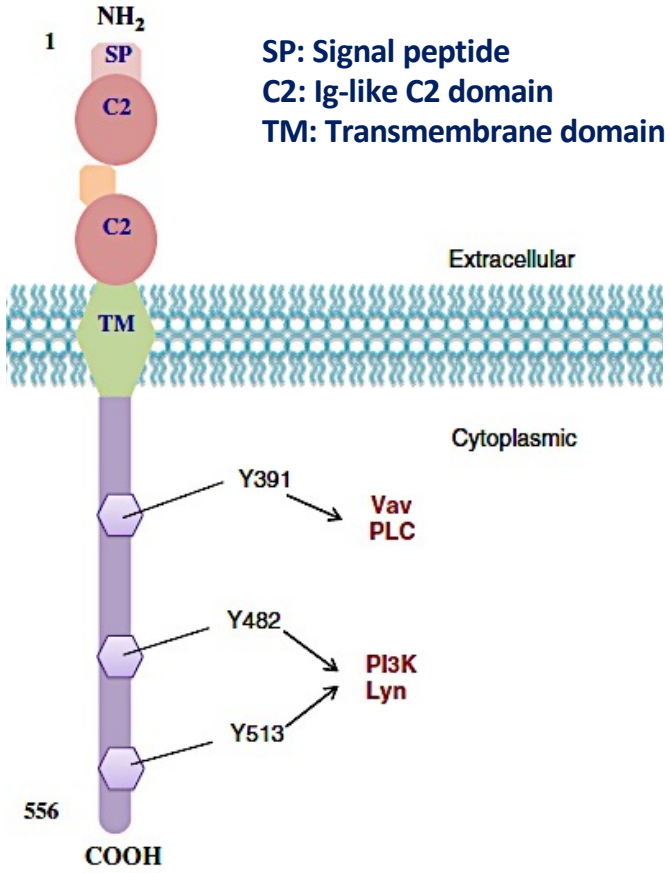
- Stable expression on target cells
- Crucial role in malignant cell biology
- Higher, deregulated expression in malignant cells vs. normal tissues

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



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

CD19 molecular structure



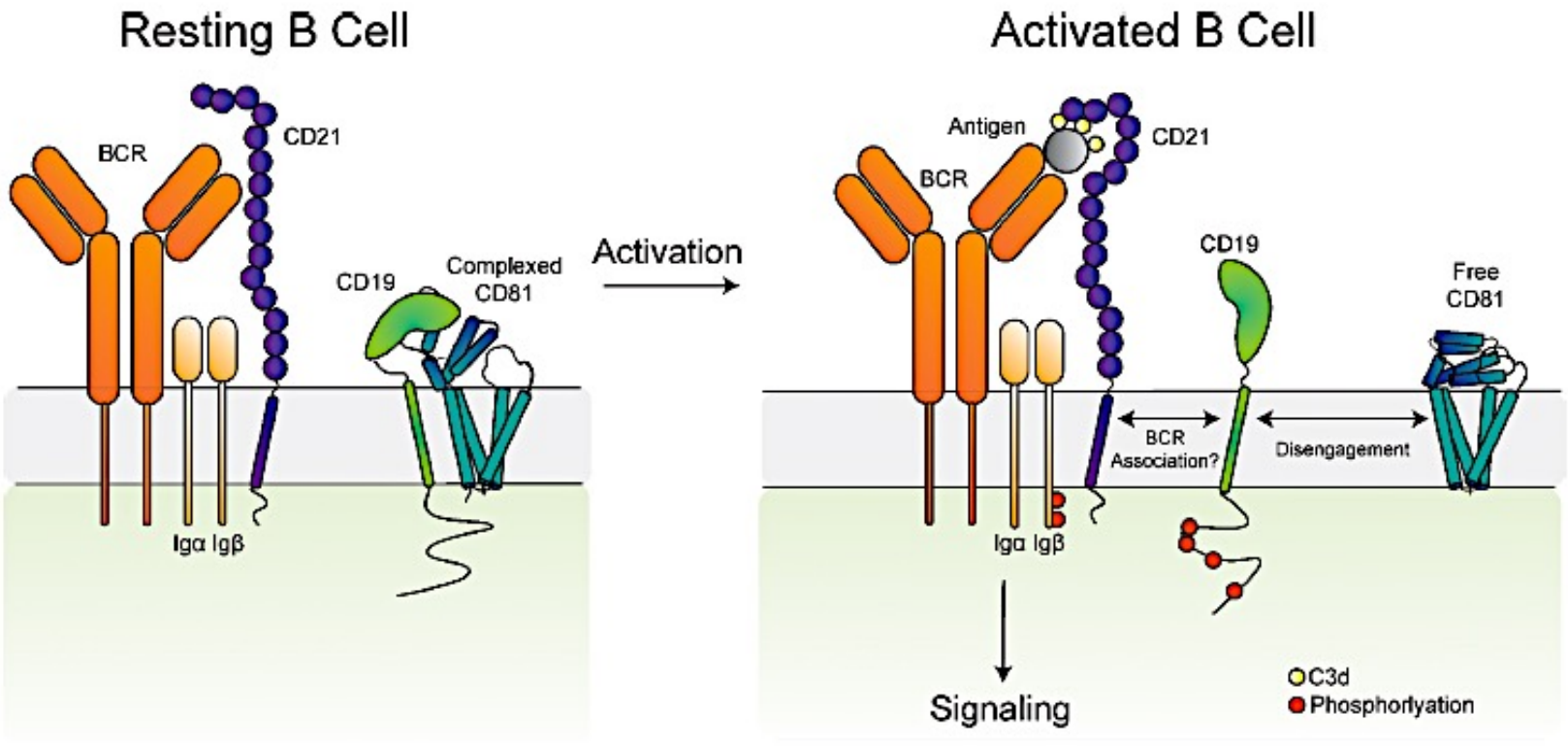
SP: Signal peptide
C2: Ig-like C2 domain
TM: Transmembrane domain

- 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**
  1. The extracellular element with **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
  2. A single transmembrane domain
  3. 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

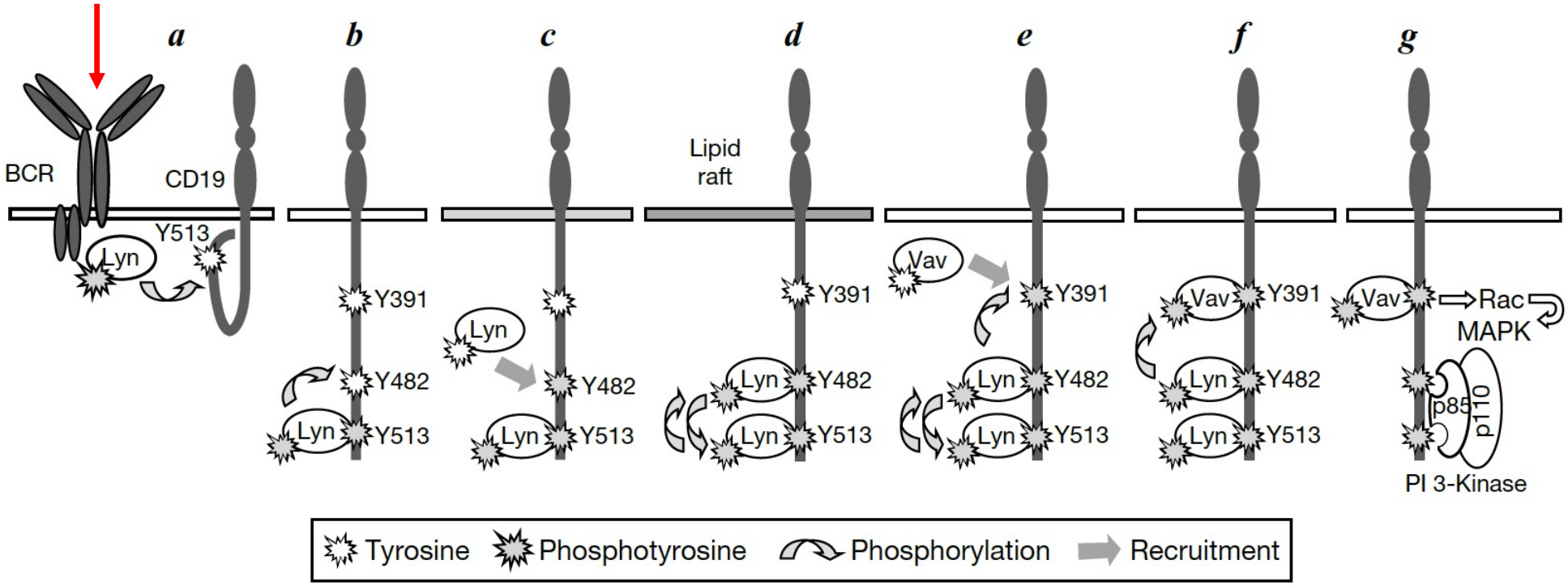
Maintenance of CD19 expression is expected as CD19 is part of a multimeric complex



Susa et al. eLife 2020;9:e52337

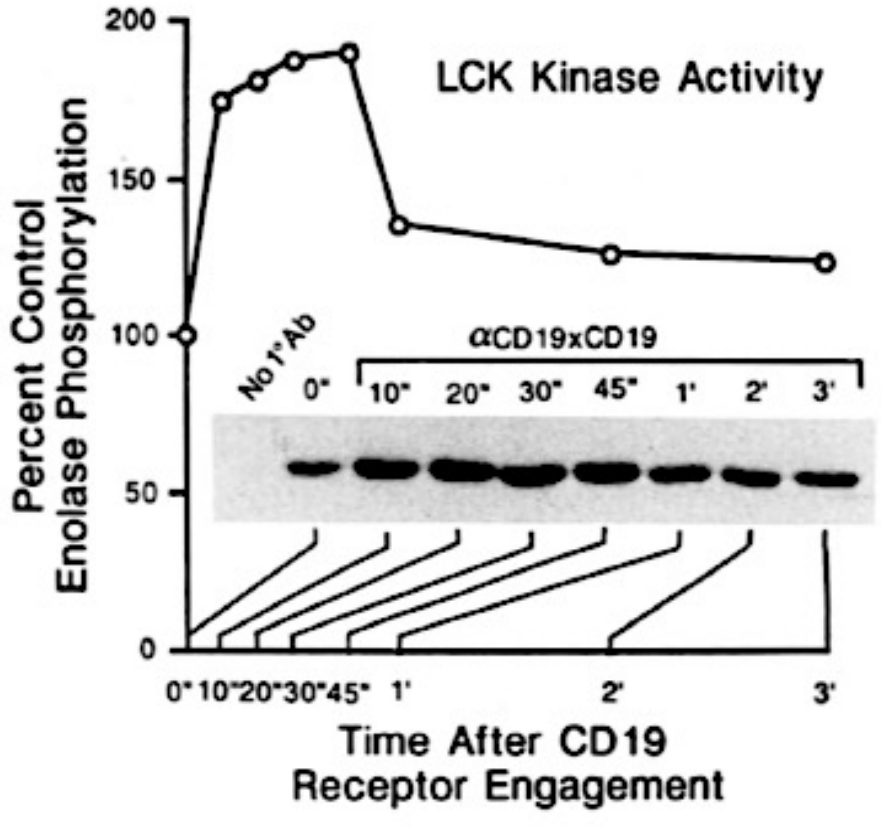
CD19 associated signaling complex

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

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

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
- Recent studies have constructed one model of lymphomagenesis involving CD19 and the proto-oncogene c-Myc
- Dysregulation in these regulators subsequently enhance lymphomagenesis

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

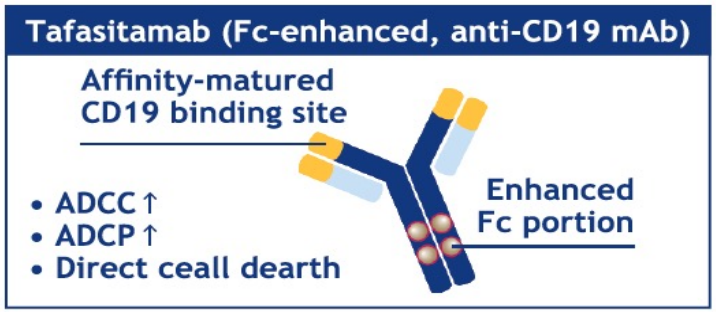
Expression levels of CD19 and CD22 on cell lines

	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

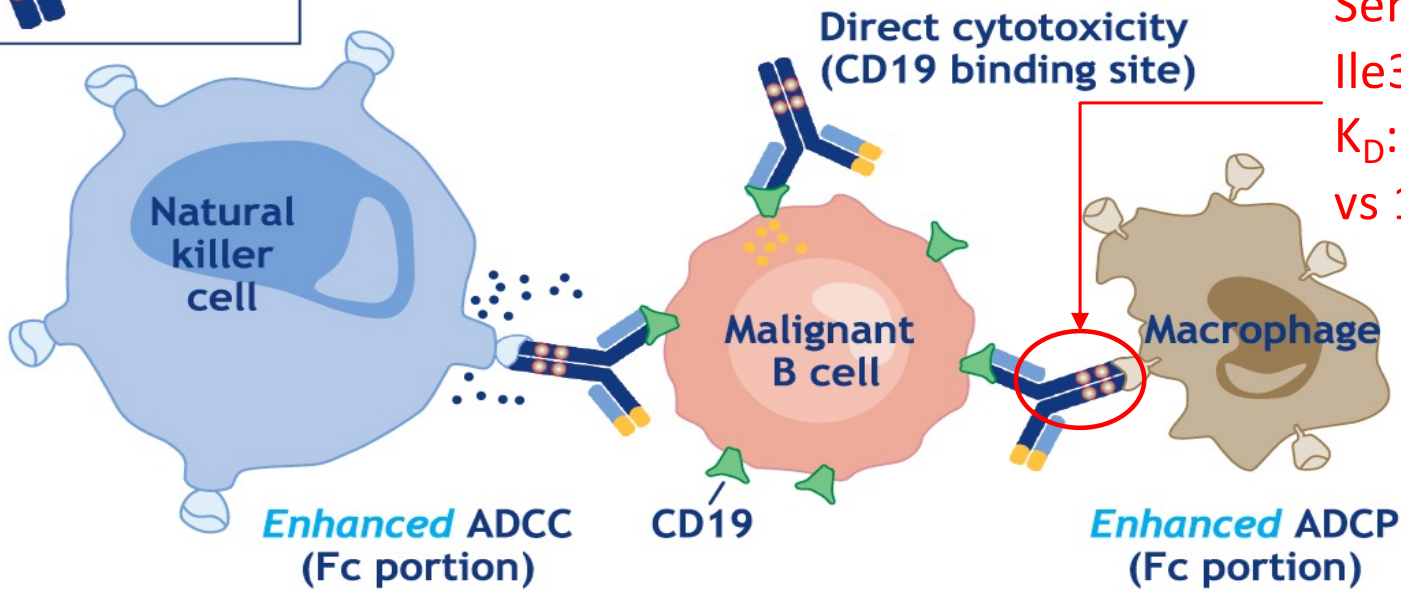
*Median fluorescence intensity (MFI)

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

Mode of action of tafasitamab

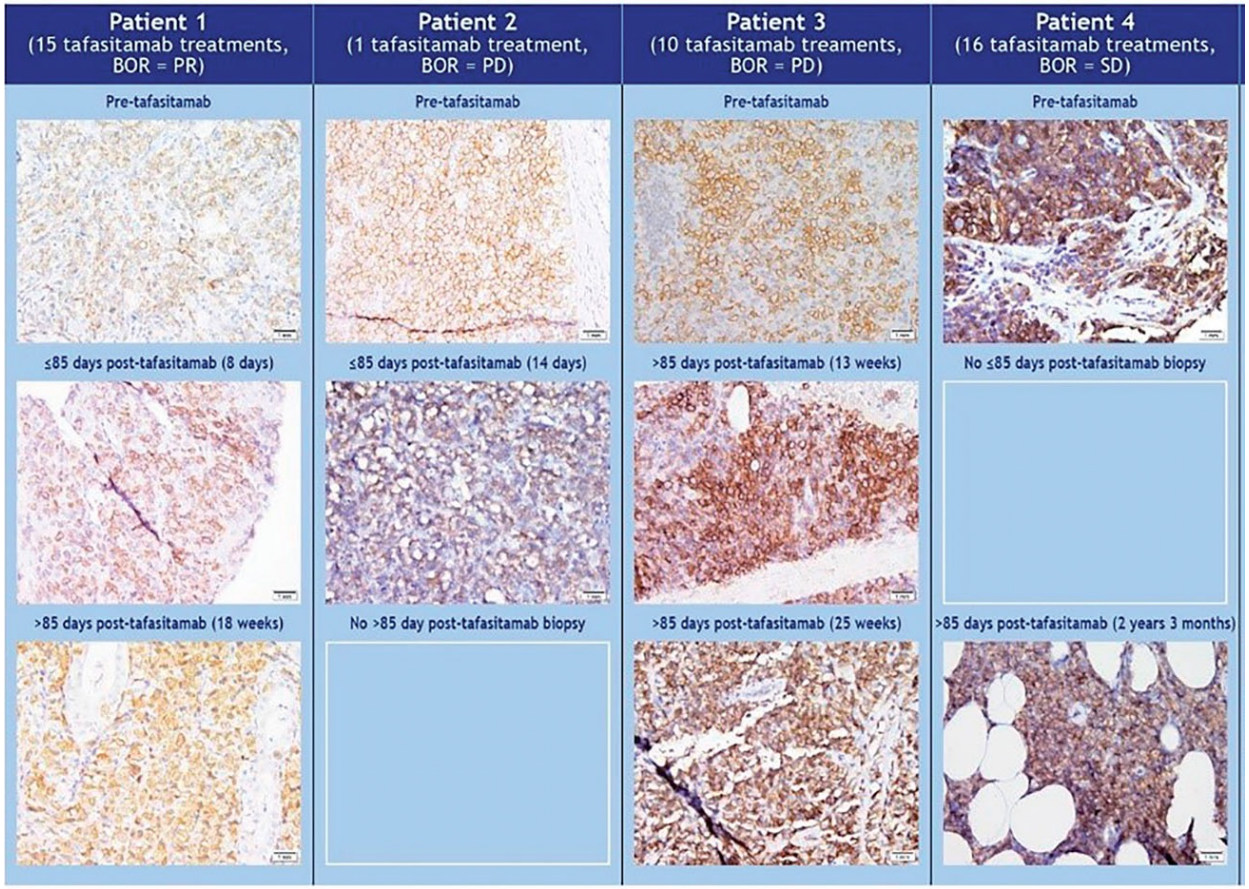


KD and affinity are inversely related. A high affinity interaction is characterized by a low KD



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

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



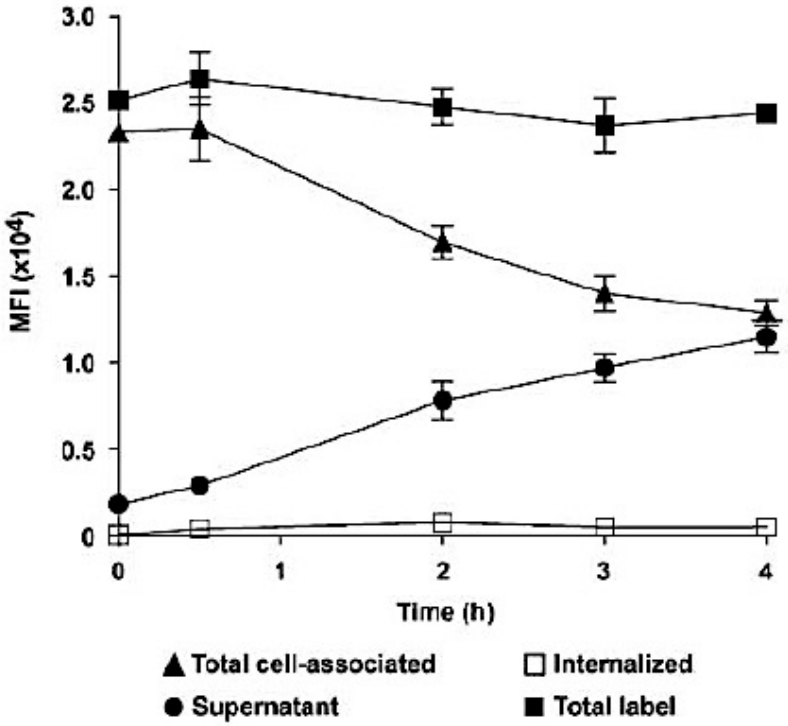
Duell J et al. Leuk Lymphoma 2022;63(2):468-472

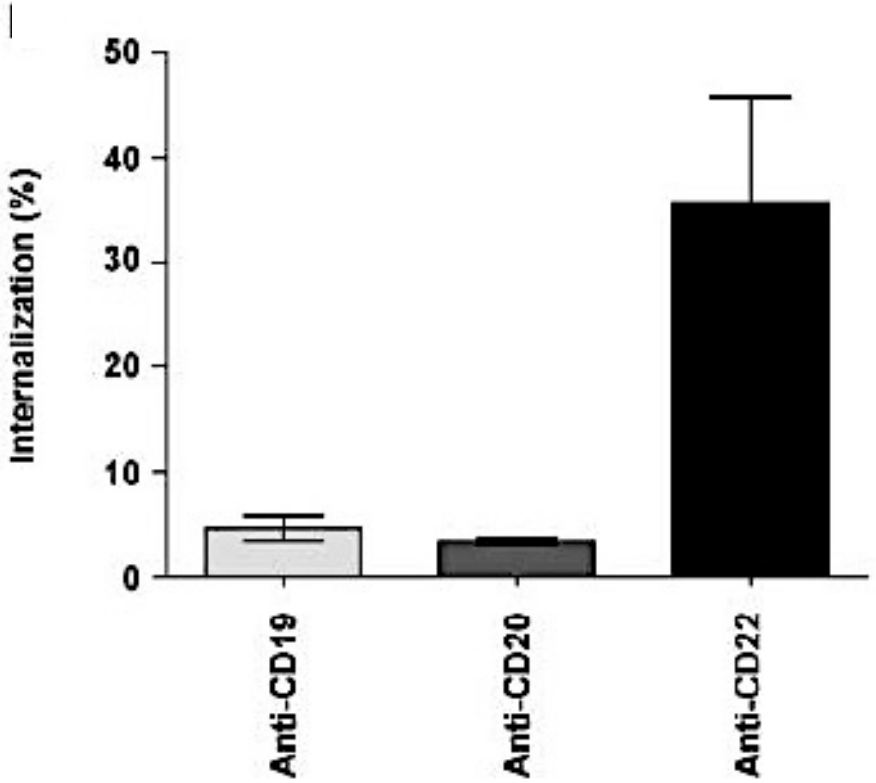
CD19 expression is maintained in DLBCL patients after treatment with tafasitamab plus lenalidomide

- 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

Tafasitamab induces minimal receptor internalization





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

Masking or simply a mechanism of resistance to treatment?

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

Taylor & Francis
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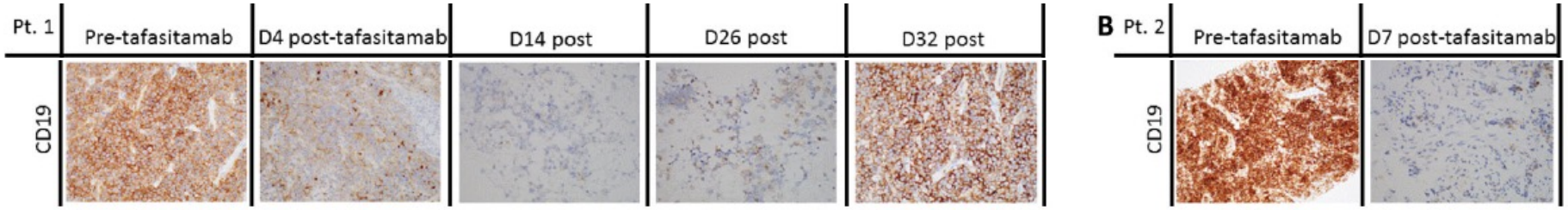
Check for updates

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

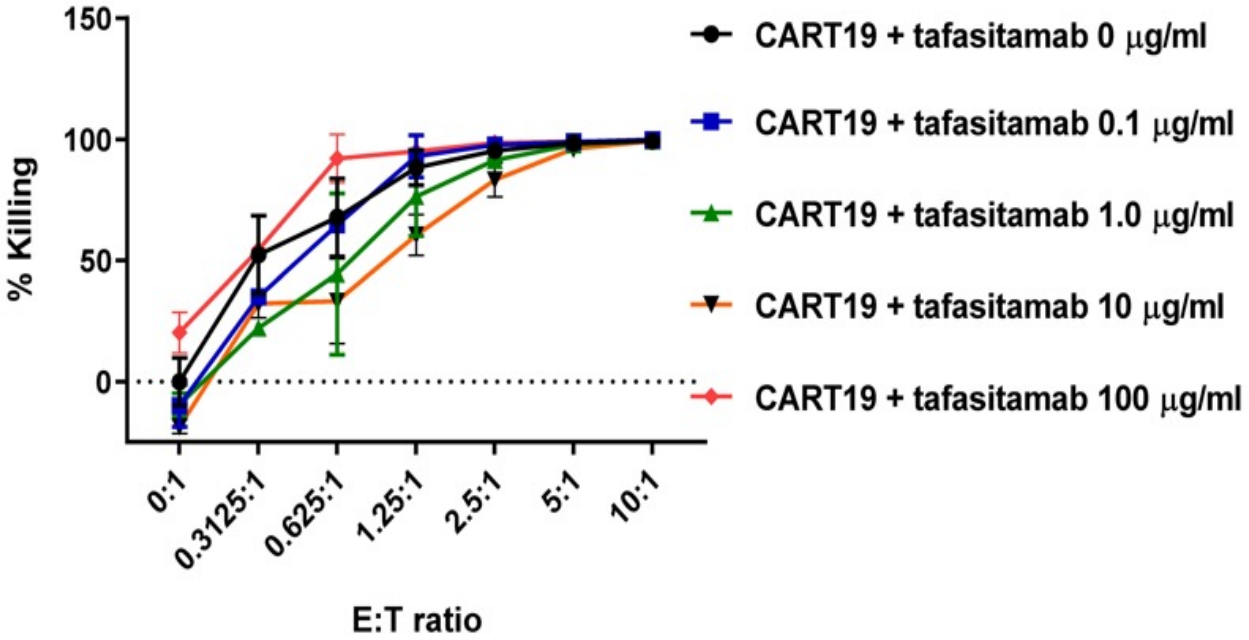
Kelly N. Fitzgerald[a], Andres E. Quesada[b], Gottfried von Keudell[a], Sandeep Raj[a], Natasha E. Lewis[b], Ahmet Dogan[c], Gilles Salles[a] and M. Lia Palomba[a]



The conclusions of the previous article are highly speculative and this is why

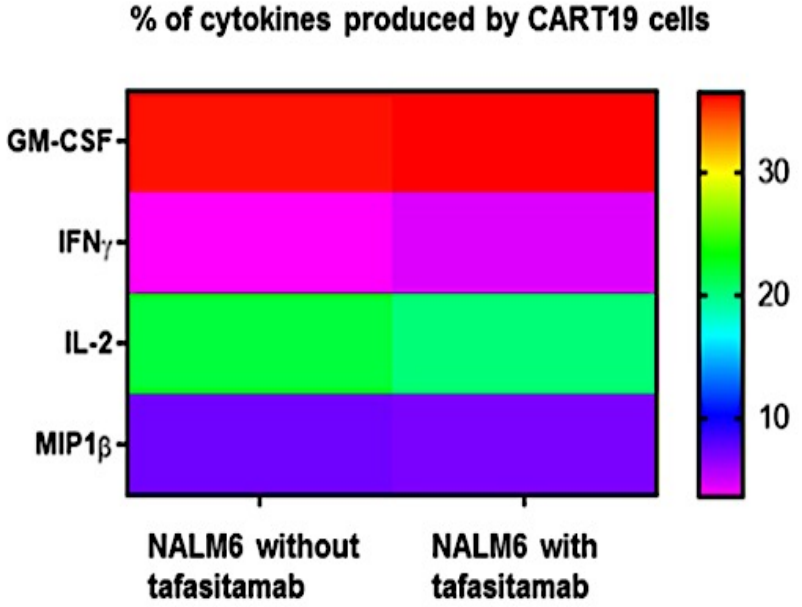
1) Disappearance of CD19 may simply be dependent on target dowregulation, which is a typical mechanism of resistance.
2) In a pre-clinical study, the presence of tafasitamab bound to the CD19 antigen did not affect important CART cell functions such as antigen specific killing, degranulation, cytokine production or proliferation of CART19 (Horvei P et al. Blood 2019;134 (Suppl1): 2859).
3) Pharmacokinetics of tafasitamab indicates a decrease of antibody concentrations below threshold 3 weeks after treatment discontinuation.

Targeting of CD19 by tafasitamab does not impair CD19 directed CART cell activity in vitro



CART cells exibits potent antigen specific cytotoxicity in the presence of tafasitamab

JEKO: mantle cell lymphoma cell line

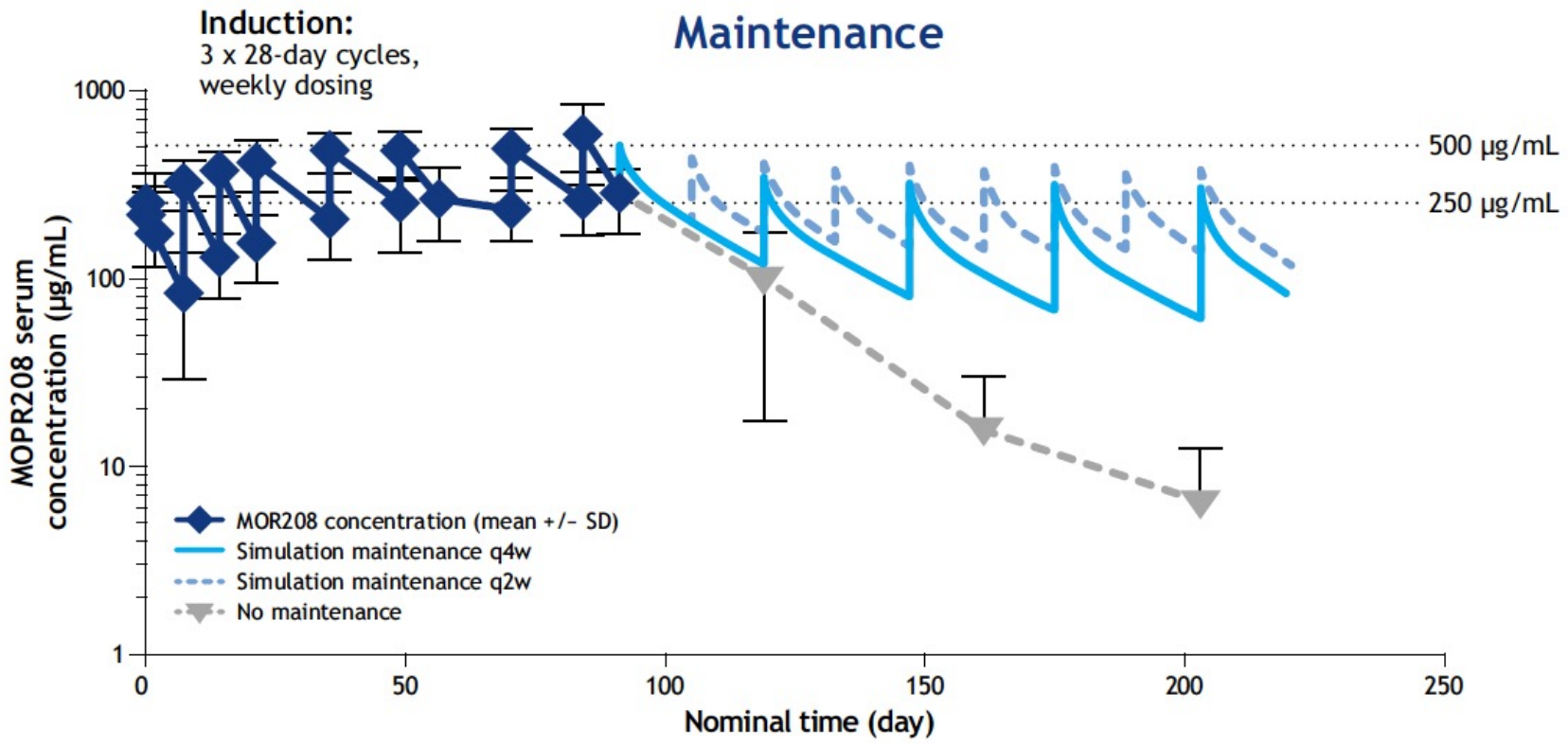


Tafasitamab does not impair antigen-specific degranulation and cytokine production by CART cells

NALM6: pre-B cell leukemia

Horvei P et al. Blood 2019;134 (Suppl. 1): 2859

Pharmacokinetics of tafasitamab



Salles G et al. Expert Opinion Biol Ther 2021;21:455-463

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.