

Eppur si muove...

La terapia nel MONDO LINFOMI

***Il CD19 come target
terapeutico nel DLBCL***

Romano Danesi



CATANIA, 11 LUGLIO 2022

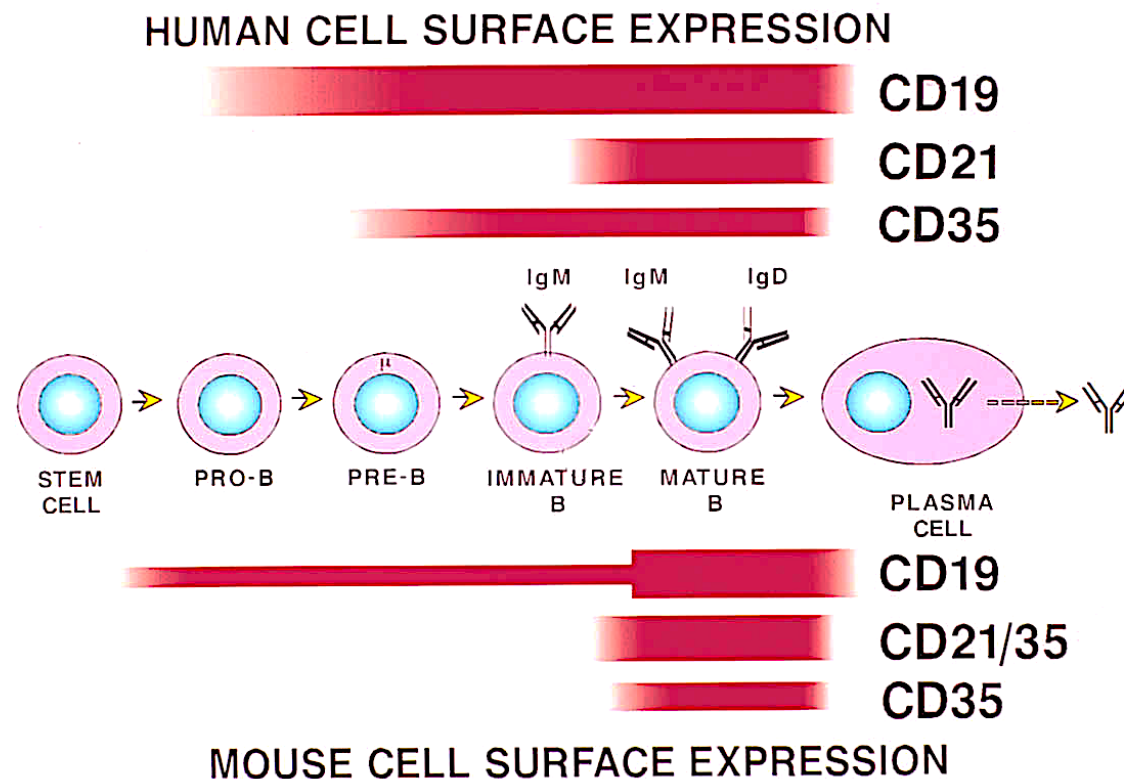
Disclosures

- *Consultant:*
 - *MSD*
 - *Lilly*
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 - *Gilead*
 - *BeiGene*
 - *Seagen*
- *Consultant:*
 - *InCyte*
 - *Pfizer*
 - *Novartis*
 - *Roche*

Characteristics of an ideal target

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

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

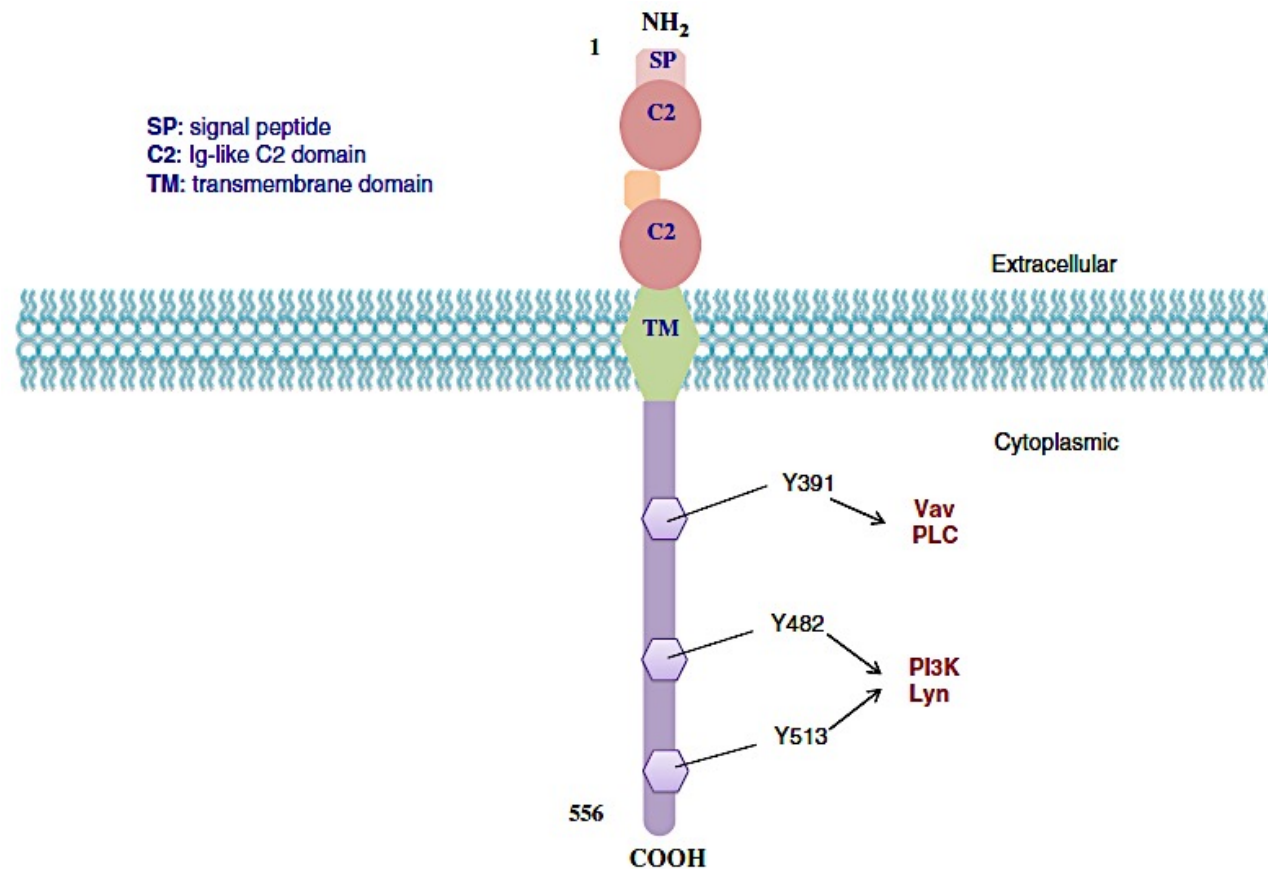


Expression levels of CD19 and CD22 on cell lines

	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)

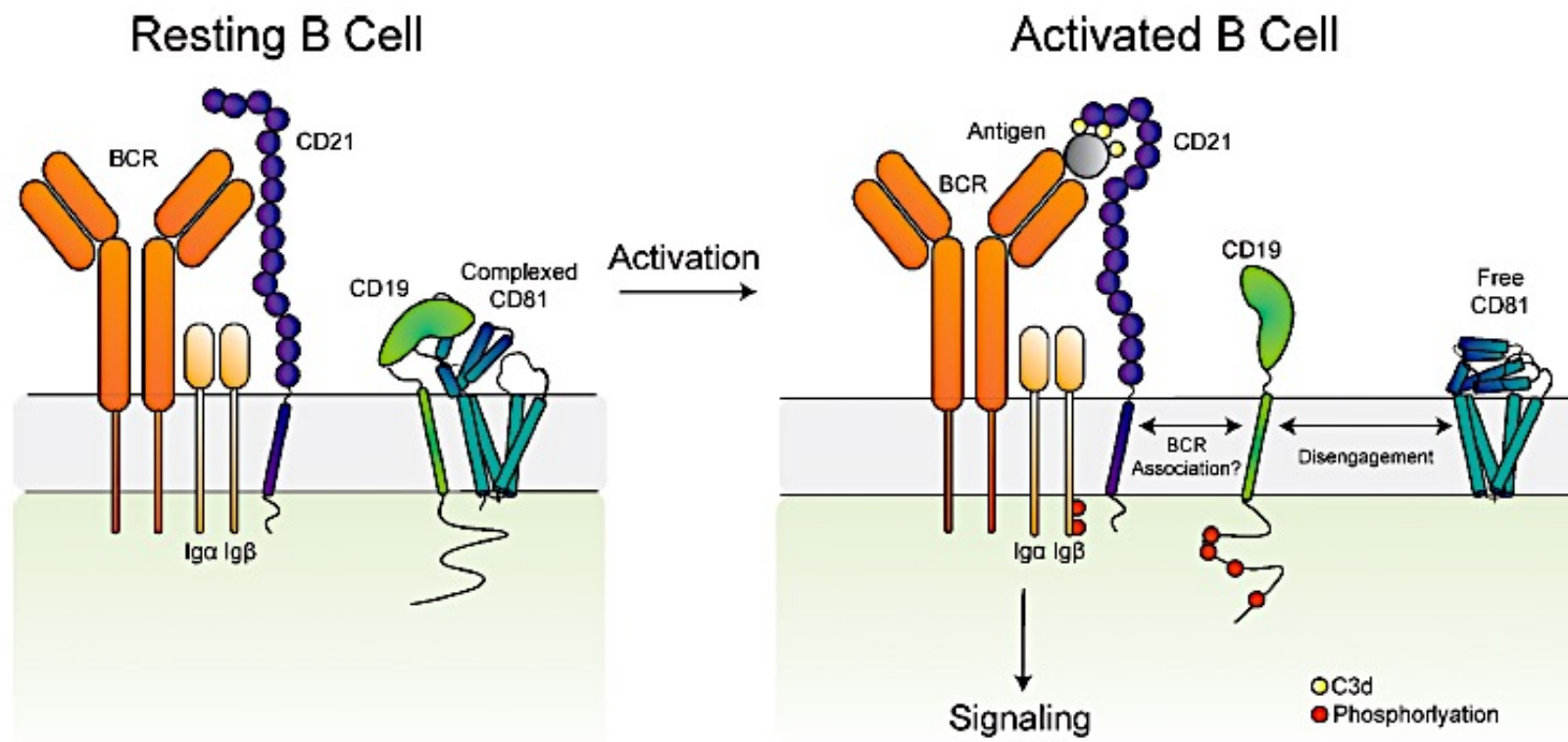
CD19 molecular structure



CD19 molecular structure

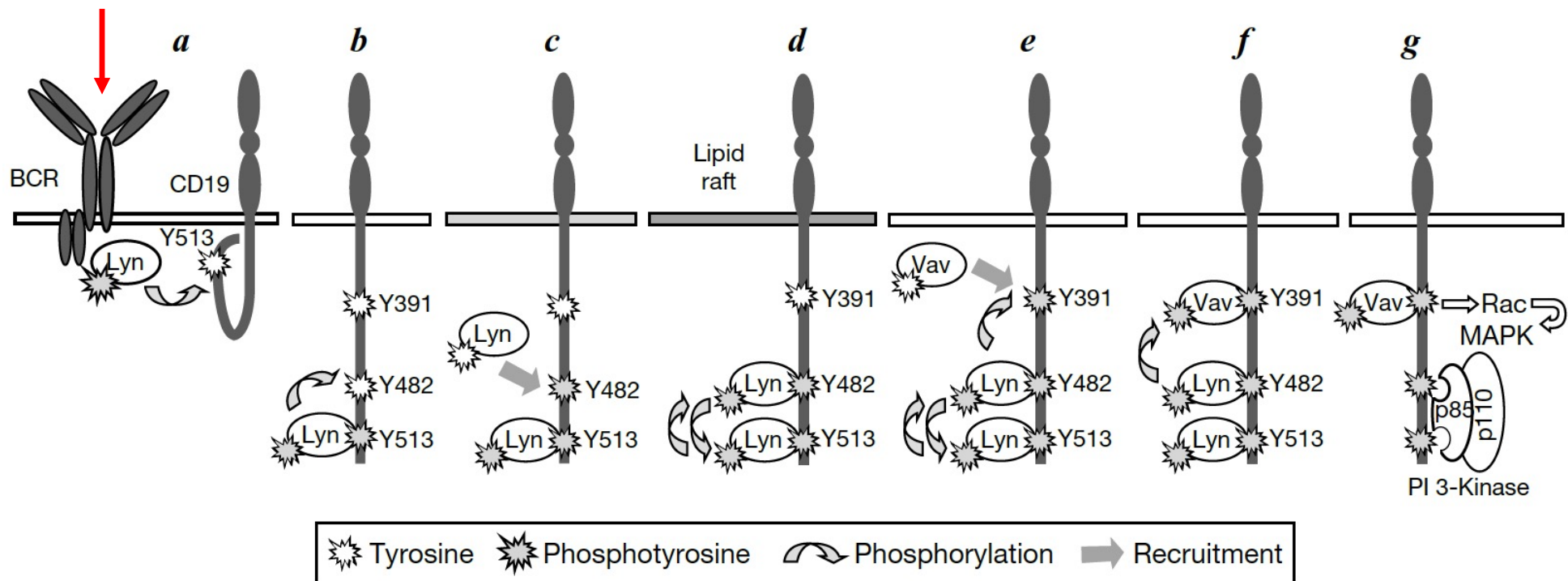
- The human CD19 antigen is a 95 kd transmembrane glycoprotein belonging to the Ig superfamily
- CD19 has a single transmembrane domain, a cytoplasmic C-terminus, and extracellular N-terminus.
- The extracellular domain contains two C2-type Ig-like domains.
- The biologic functions of CD19 are dependent on three cytoplasmic tyrosine residues – Y391, Y482 and Y513.

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

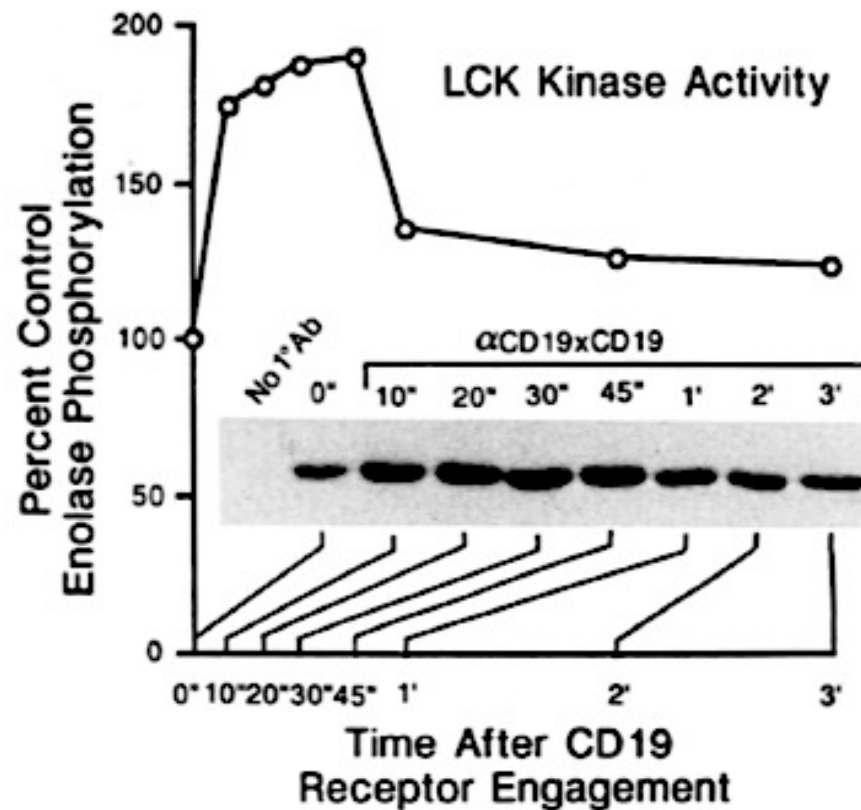


CD19 associated signaling complex

Stimulation



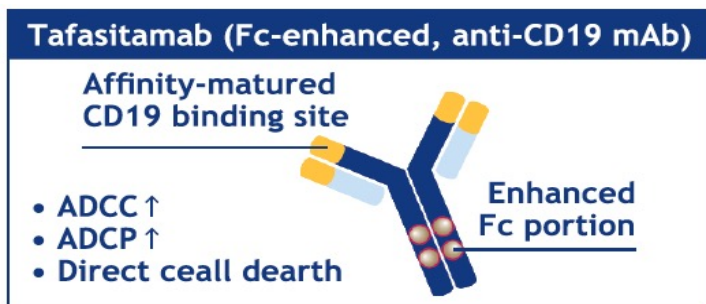
Time course of Src family PTK activation after cross-linking of CD19 receptor molecules with an anti-CD19xCD19 homoconjugate



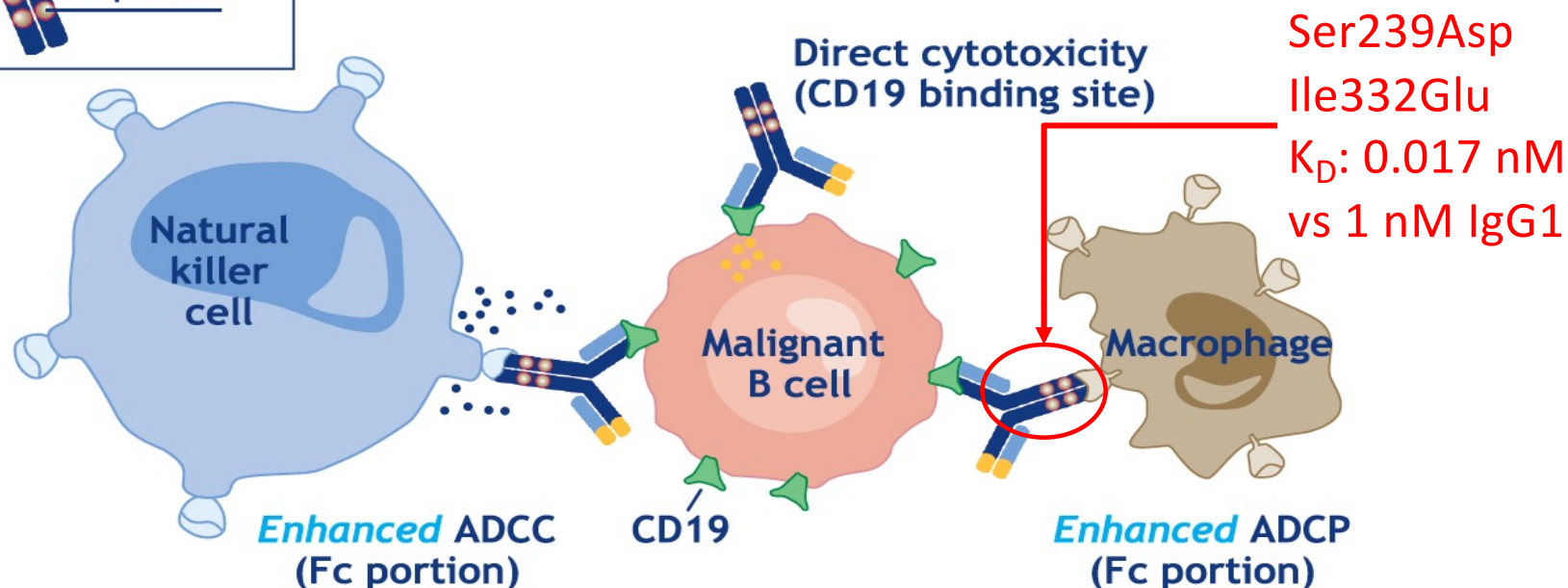
CD19 disease association

- CD19 expression is highly conserved on most B cell tumors.
- The majority of B cell malignancies express CD19 at normal to high levels.
- Upregulated CD19 expression and phosphorylation, induced by constitutive c-Myc, serve to further promote and stabilize c-Myc signaling and induce lymphomagenesis.

Mode of action of tafasitamab



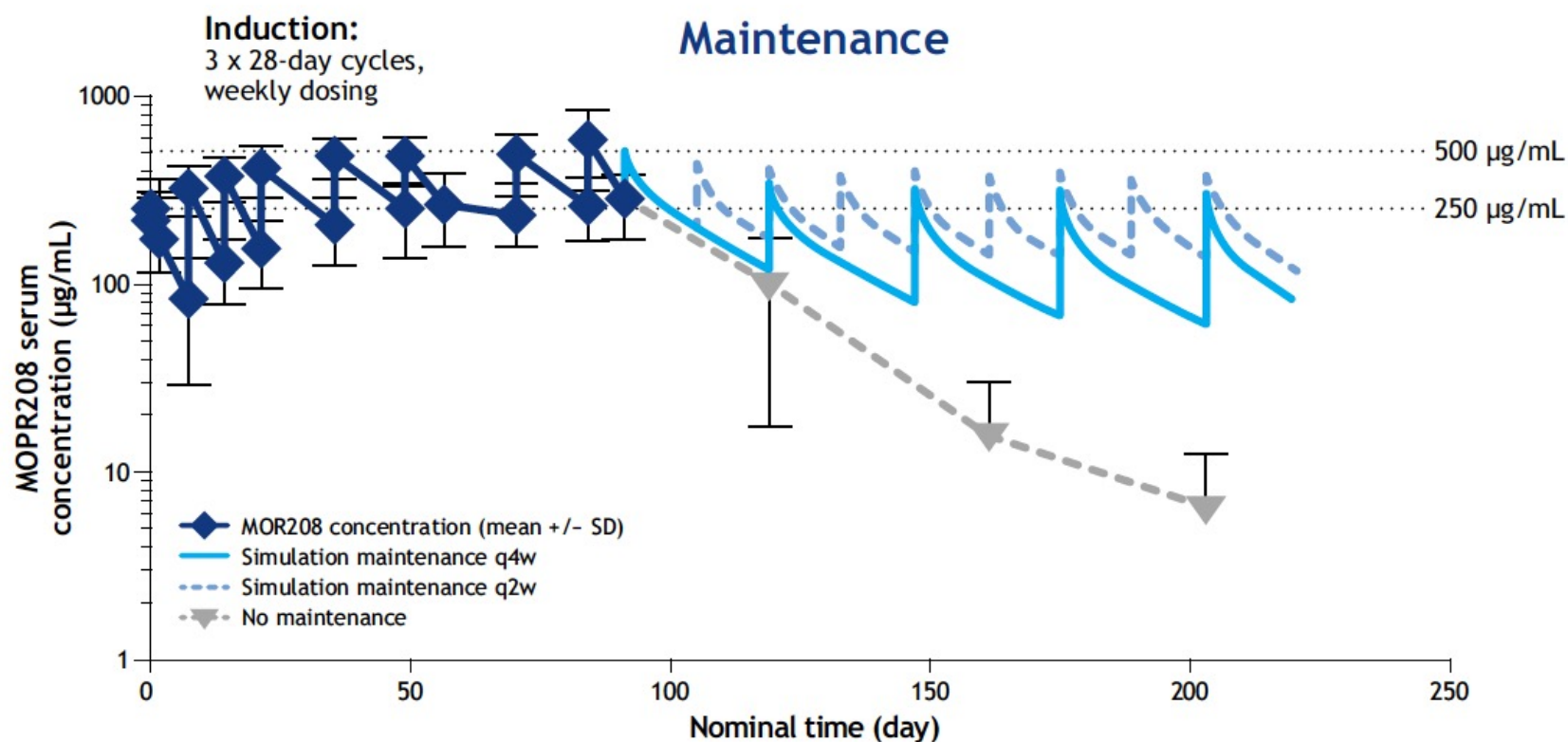
KD and affinity are inversely related. A high affinity interaction is characterized by a low KD



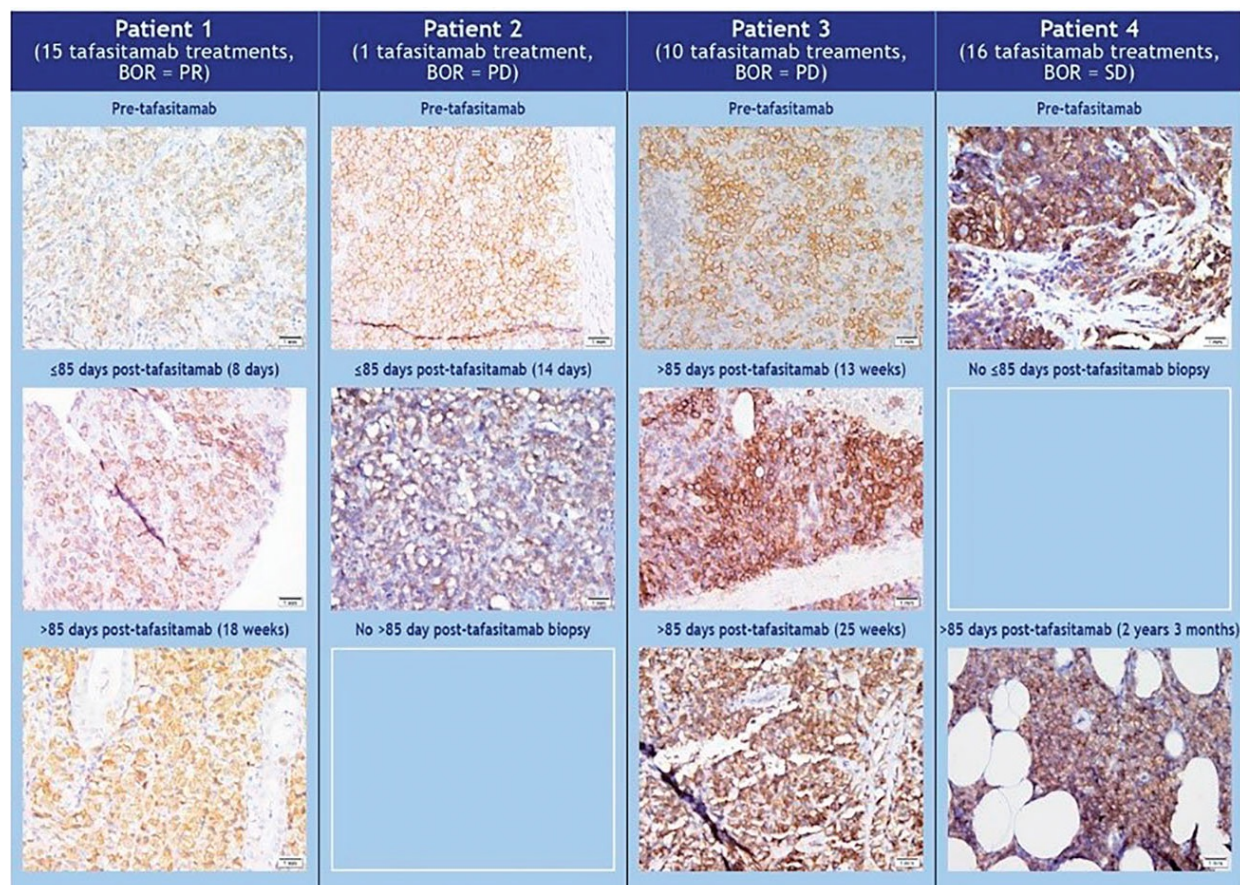
Zalevsky J et al. Blood. 2009;113:3735-3743

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

Pharmacokinetics of tafasitamab



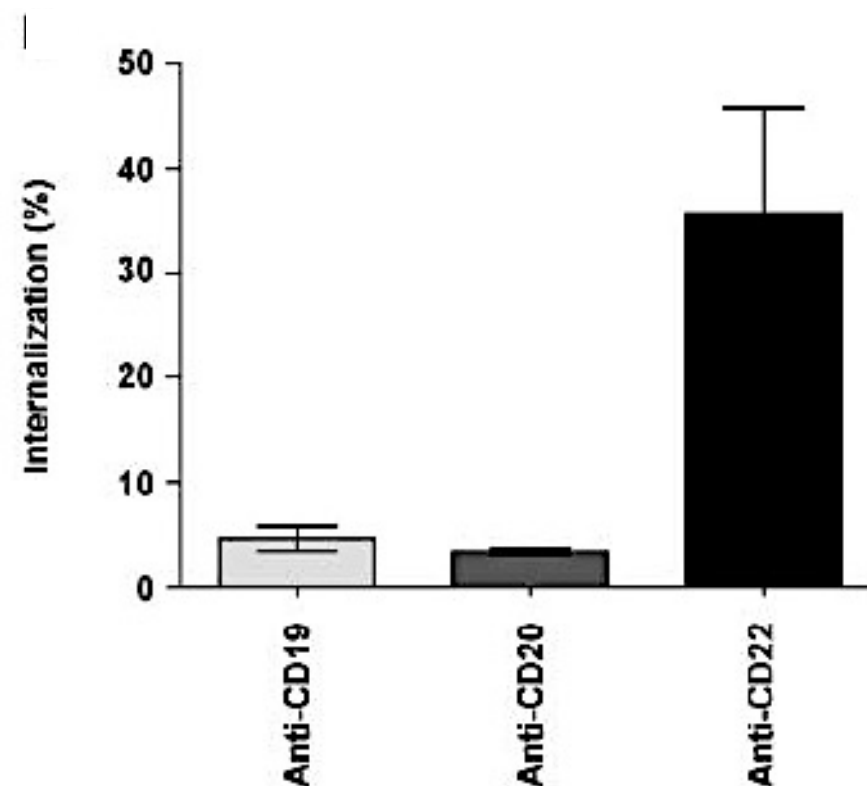
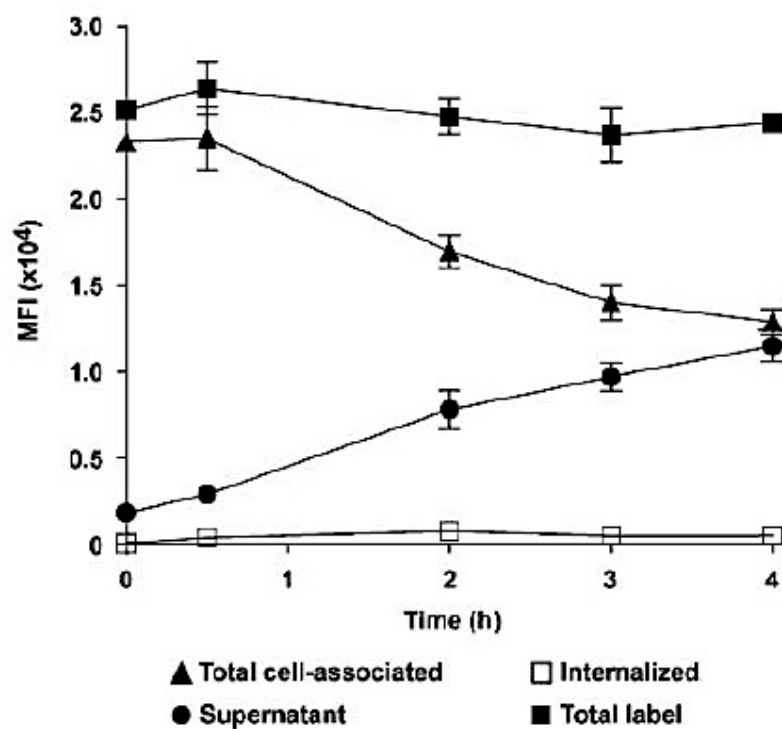
CD19 expression is maintained in DLBCL patients after treatment with tafasitamab plus lenalidomide



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.

Tafasitamab induces minimal receptor internalization



Masking or simply a mechanism of resistance to treatment?

LEUKEMIA & LYMPHOMA

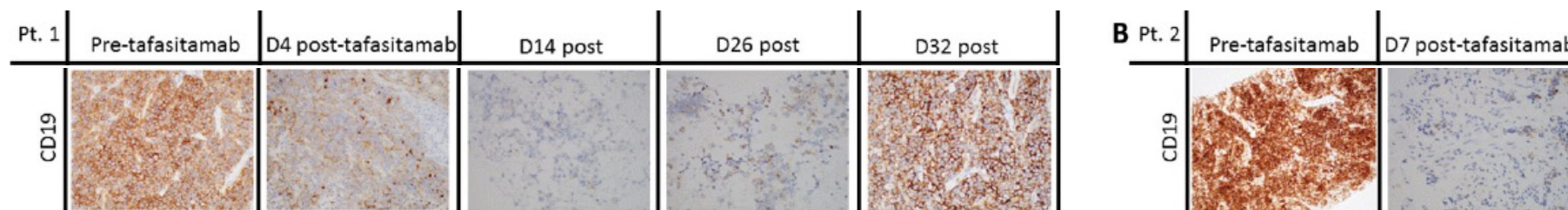
<https://doi.org/10.1080/10428194.2021.1992622>Taylor & Francis
Taylor & Francis Group

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

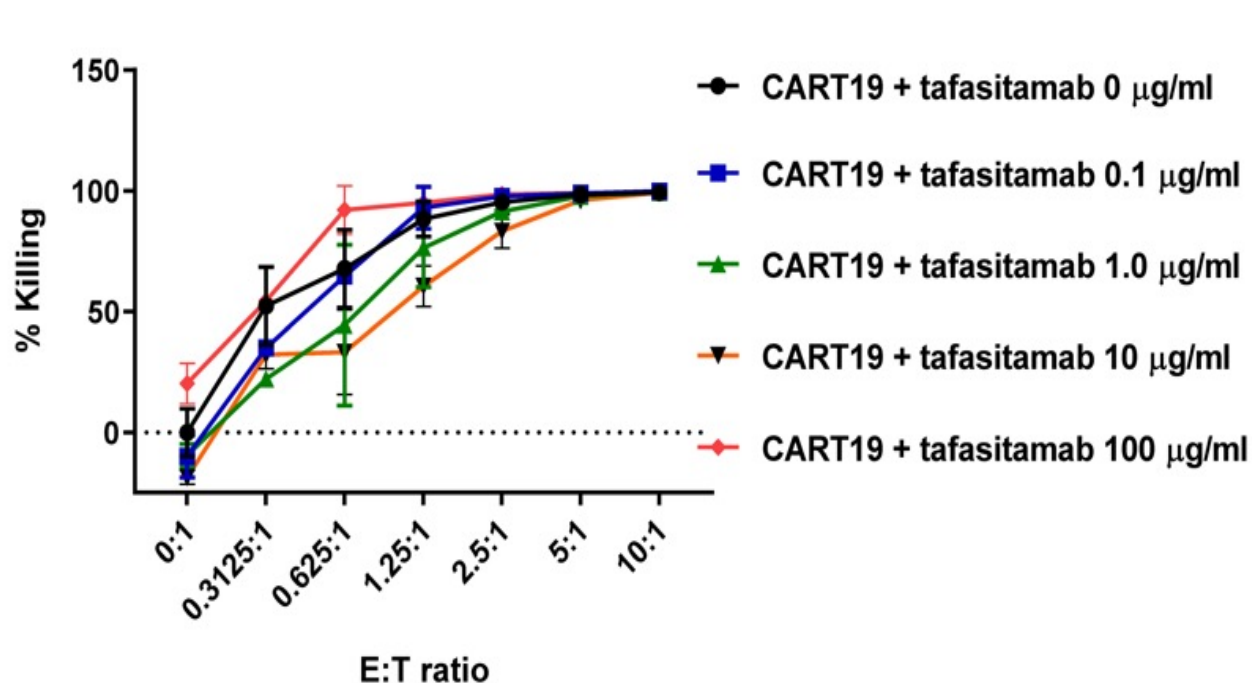
Kelly N. Fitzgerald^a , Andres E. Quesada^b, Gottfried von Keudell^a, Sandeep Raj^a, Natasha E. Lewis^b, Ahmet Dogan^c, Gilles Salles^a and M. Lia Palomba^a



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

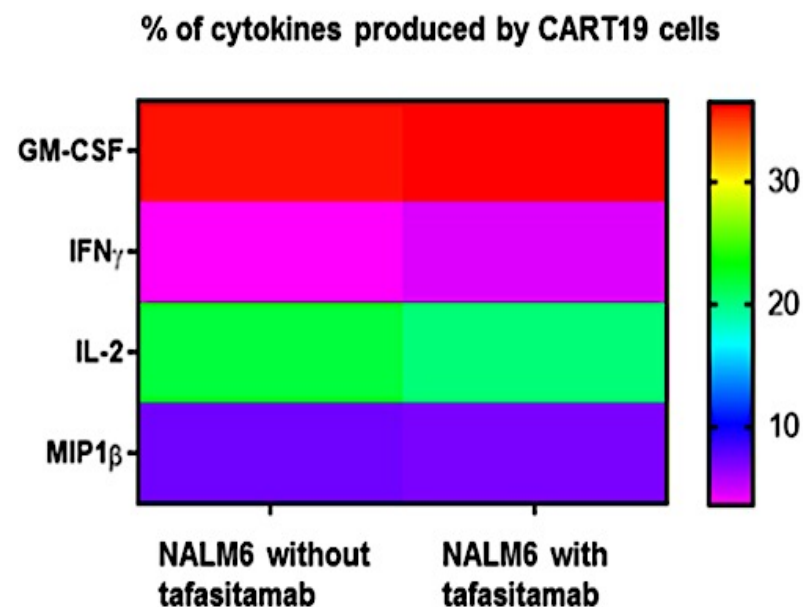
- 1) Disappearance of CD19 may simply be dependent on target downregulation, which is a typical mechanism of resistance.
 - 2) In a pre-clinical study, the presence of tafasitamab bound to the CD19 antigen did not affect important CART cell functions such as antigen specific killing, degranulation, cytokine 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 exhibit potent antigen specific cytotoxicity in the presence of tafasitamab
JEKO: mantle cell lymphoma cell line

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



Tafasitamab does not impair antigen-specific degranulation and cytokine production by CART cells
NALM6: pre-B cell leukemia

Anti-CD19 CAR T-cell therapy remission despite prior anti-CD19 antibody Tafasitamab in relapsed/refractory DLBCL

Leukemia Research Reports 16 (2021) 100260



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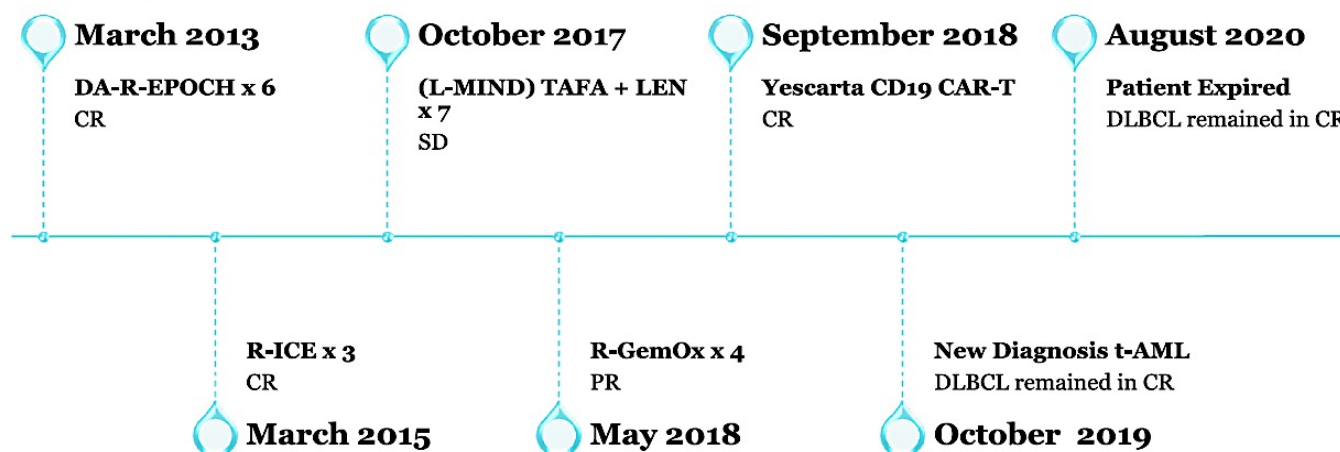


Anti-CD19 CAR T-cell therapy remission despite prior anti-CD19 antibody Tafasitamab in relapsed/refractory DLBCL

Nadeem Tabbara^{a,*}, Daria Gaut^b, Caspian Oliai^b, Tara Lewis^b, Sven de Vos^b

^a Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, 2020 Santa Monica Blvd, Suite 600, Los Angeles, CA 90404, USA

^b Division of Hematology/Oncology, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA



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.