Alternatives to anti-CD19 CAR-T cells for optimizing B-cell depletion in autoimmune diseases

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Autoimmune Diseases INSERM U1184,
Université Paris-Saclay

Conflicts of interest disclosure

- Honoraria/consultancy:
  - Astra Zeneca
  - Bristol-Myers Squibb,
  - Galapagos
  - GlaxoSmithKline,
  - Novartis,
  - Pfizer Inc.,

Outline

- Improving B-cell depletion induced by rituximab
  - Rituximab + Belimumab
  - Obinutuzumab
  - Ianalumab
- Targeting plasma cells:
  - Daratumumab
- Bispecific antibodies
  - In hematology
  - In autoimmune diseases

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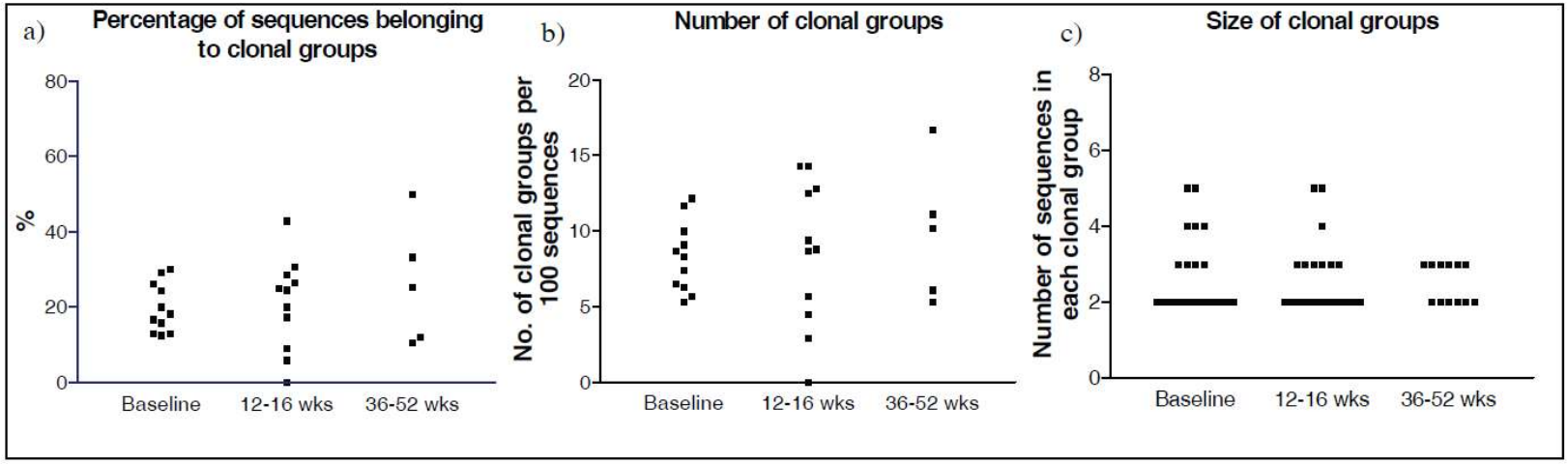
Depletion of B cells in tissue is incomplete after RTX

ARD

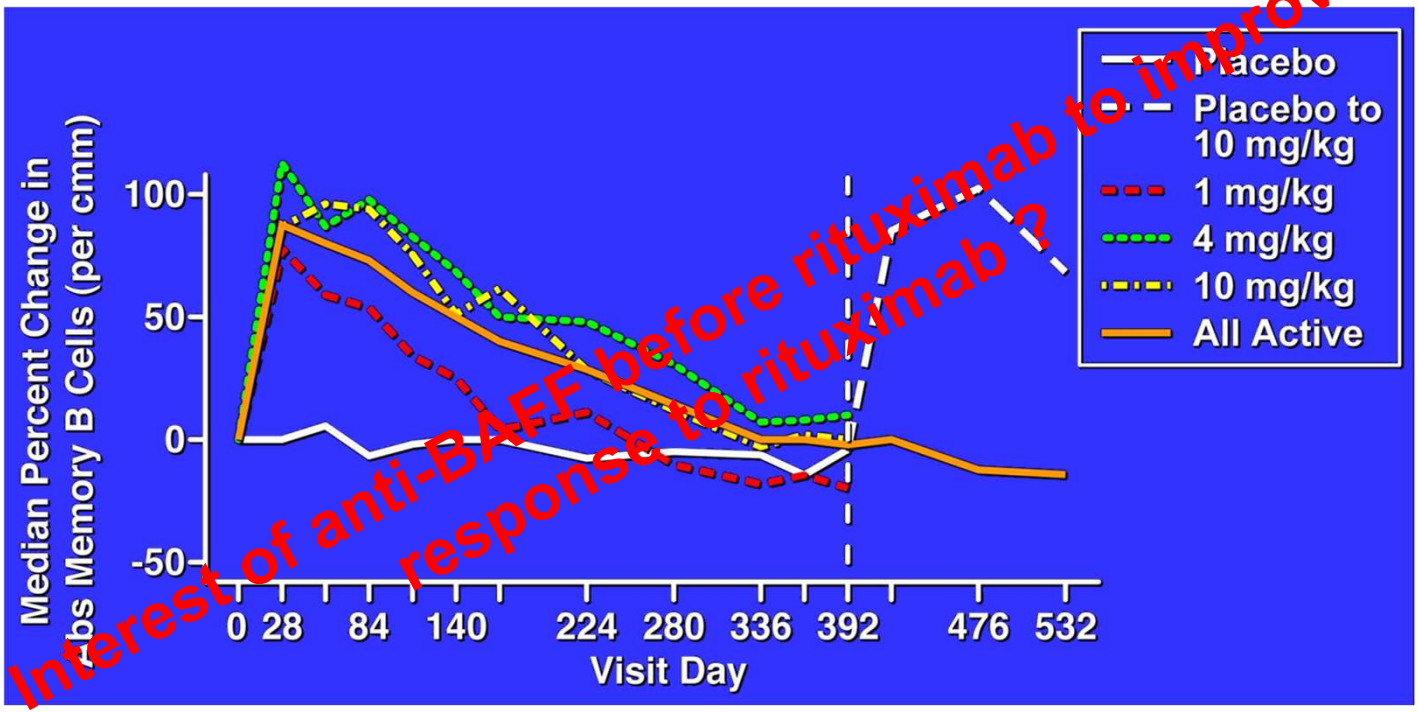
Persistence of immunoglobulin-producing cells in parotid salivary glands of patients with primary Sjögren's syndrome after B cell depletion therapy

Nishath Hamza, Hendrika Bootsma, Saravanan Yuvaraj, et al.

Ann Rheum Dis 2012 71: 1881-1887 originally published online May 21, 2012
doi: 10.1136/annrheumdis-2011-201189



Belimumab Increased CD20+/CD27+ Memory B-Cells, but Normalized By Week 52

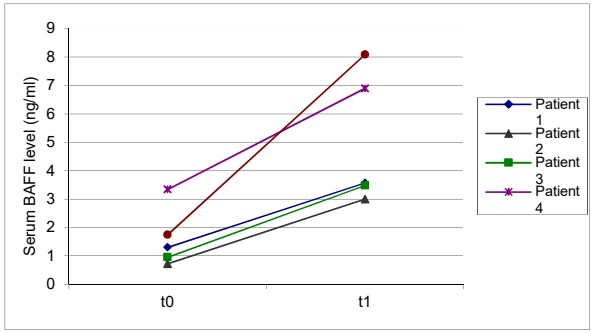


p< 0.0001 for the comparison between all active vs. placebo from Day 28 through Day 224

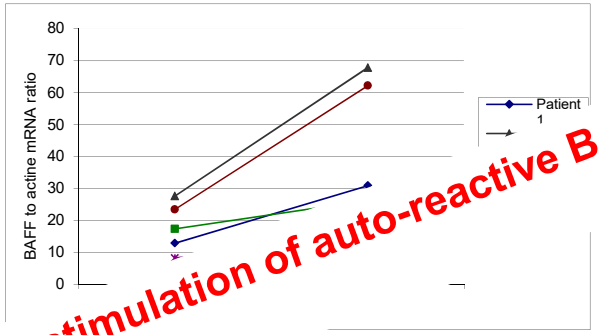
Belimumab: Phase 2 SLE Results, data from GSK

Increase in serum BAFF after rituximab

Serum BAFF

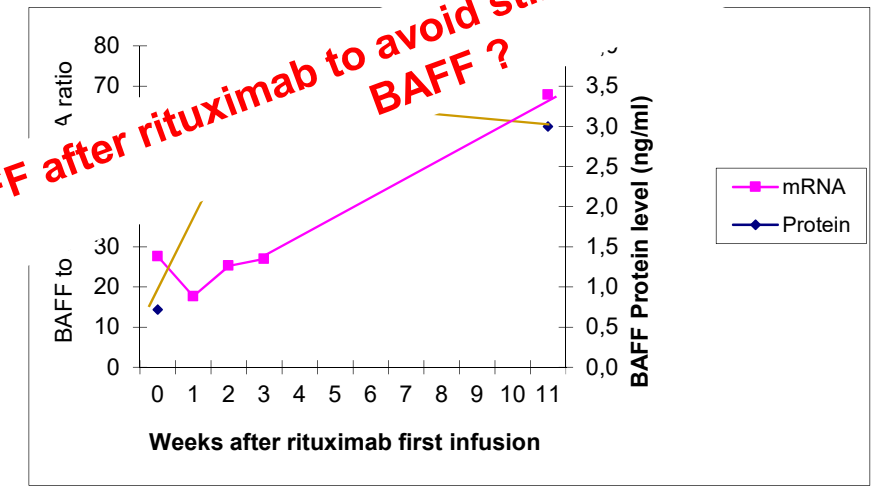


PBMC BAFF mRNA



- **2 SLE**
- **2 SS**

Interest of anti-BAFF after rituximab to avoid stimulation of auto-reactive B cells via BAFF ?



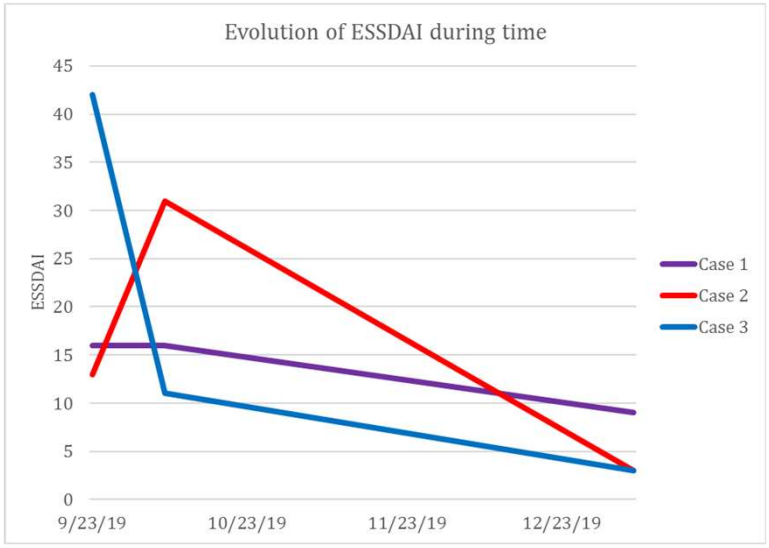
D

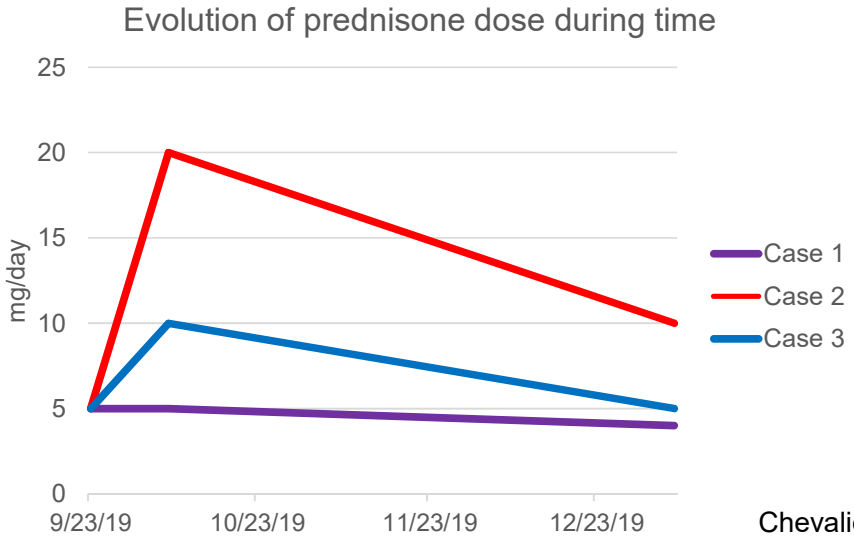
Lavie et al Ann Rheum Dis, 2006

Efficacity of a sequential treatment by anti-CD 20 monoclonal antibody and belimumab in type II cryoglobulinaemia associated with primary Sjögren syndrome refractory to rituximab alone

3 patients with Sjögren's and cryoglobunemia vasculitis refractory to different lines of treatments

History of treatments				
	First line	CYC	RTX	RTX
	Second line	RTX	CYC	RTX+CYC
	Third line	RTX+CYC	MMF	
	Fourth line	RTX	Ofatumumab+CYC	
	Fifth line	RTX followed by AZA		
	Sixth line	RTX+CYC		
	Seventh line	CYC+RTX followed by MMF		





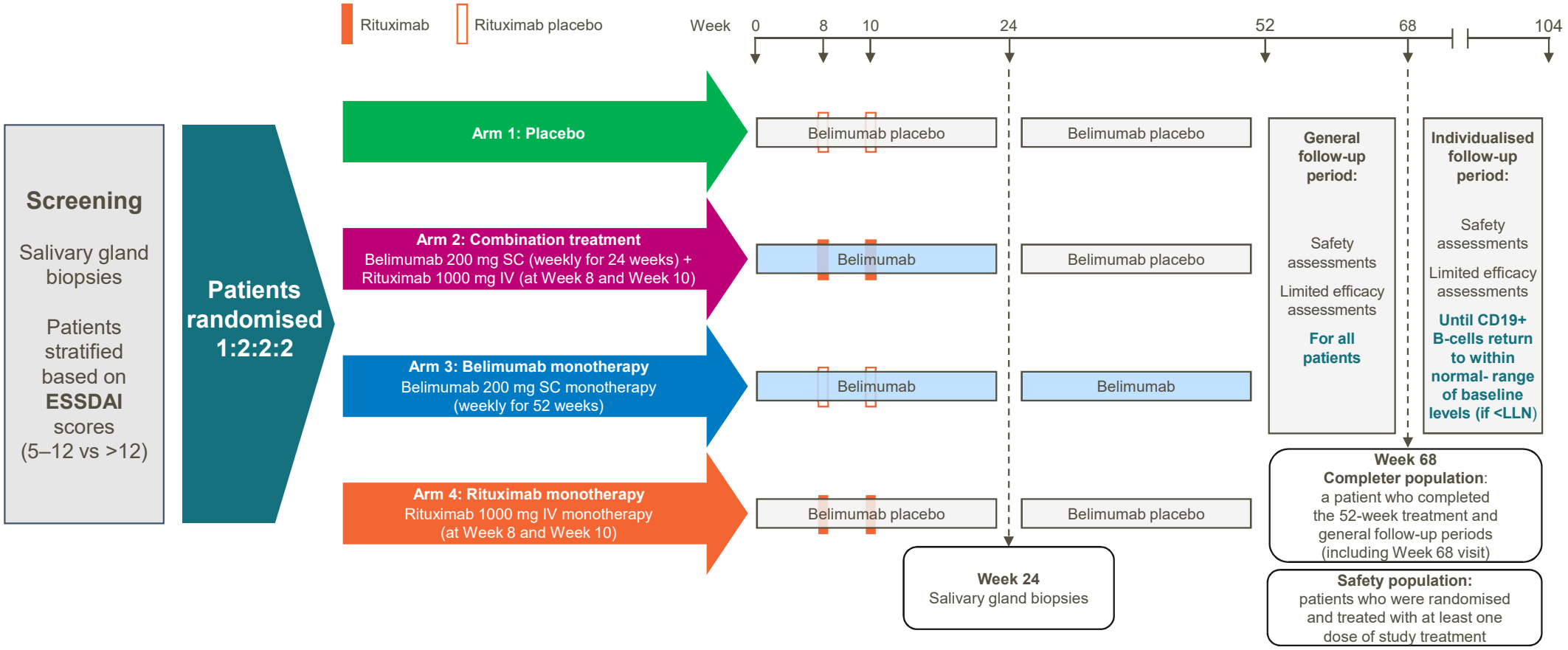
Chevalier et al. et al Ann Rheum Dis, 2020

JCI insight

A randomized, phase II study of sequential belimumab and rituximab in primary Sjögren's syndrome

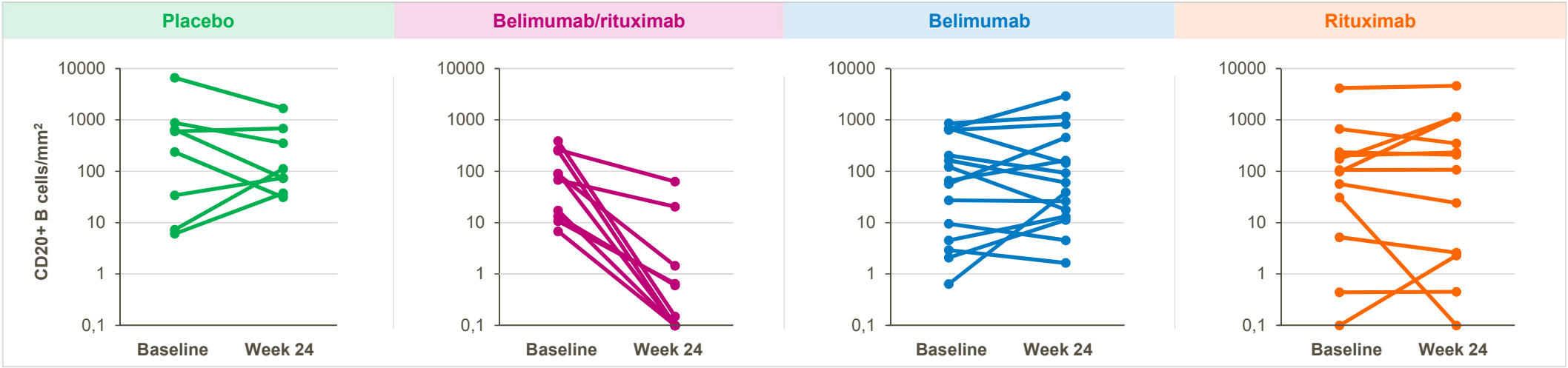
Xavier Mariette, … , David A. Roth, Paul Peter Tak

JCI Insight. 2022;7(23):e163030. https://doi.org/10.1172/jci.insight.163030.



Mechanistic Biomarker: CD20+ B-cell Depletion in Salivary Gland Biopsies (Completer Population)

In contrast with placebo, belimumab and rituximab monotherapies, salivary gland biopsies from **belimumab/rituximab** showed **near complete CD20+ B-cell depletion** (at Week 24)



	Placebo		Belimumab/rituximab		Belimumab		Rituximab	
Median (IQR) absolute number of CD20+ B cells/mm²	**418** (21–763) n=8	**93** (55–518) n=8	**88** (13–252) n=15	**0** (0–1) n=10	**66** (5–636) n=19	**61** (13–455) n=15	**106** (31–235) n=13	**158** (2–745) n=12

IQR, interquartile range

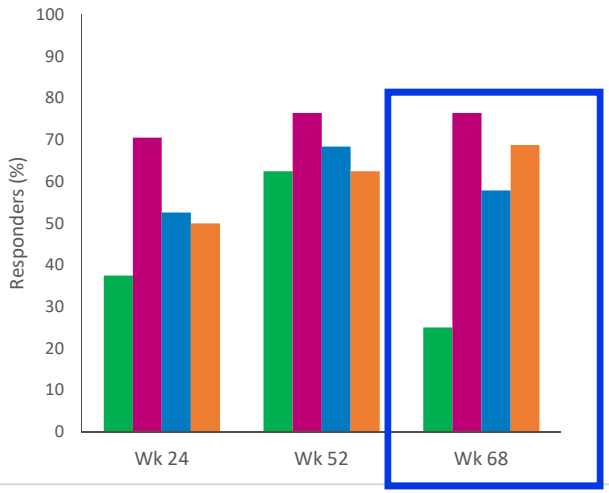
Figure: Post-hoc analysis; displays data only for patients with paired baseline and Week 24 biopsies. Minimum values are constrained to 0.1
Table: Displays all baseline and Week 24 data for completer population

Efficacy: ESSDAI Responder Analysis (Completer Population)

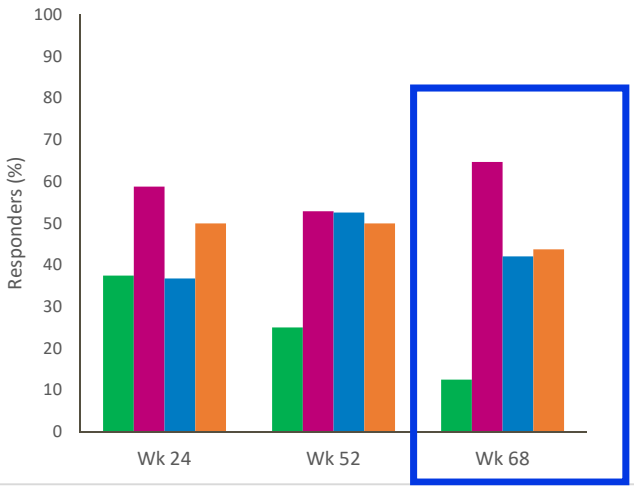
At Week 52, there was a **numerically higher proportion** of responders in the **belimumab/rituximab** group than in the placebo group; this trend was sustained to Week 68

This trend was also observed for the belimumab and rituximab groups versus the placebo group

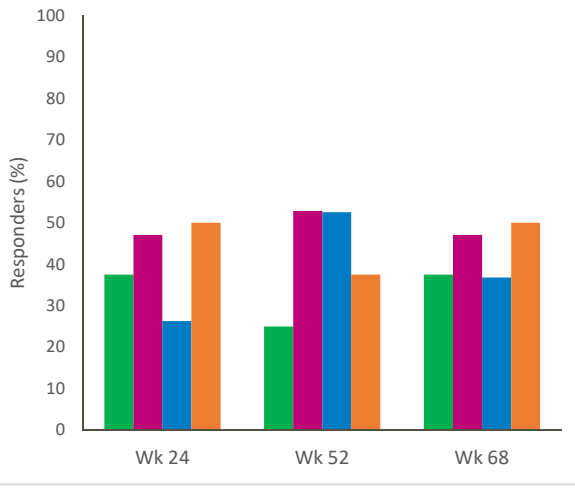
Percentage of ESSDAI responders (≥3-point improvement vs. baseline)



Percentage of ESSDAI responders (≥5-point improvement vs. baseline)



Percentage of ESSDAI responders (total score <5)



Placebo · Belimumab/rituximab · Belimumab · Rituximab

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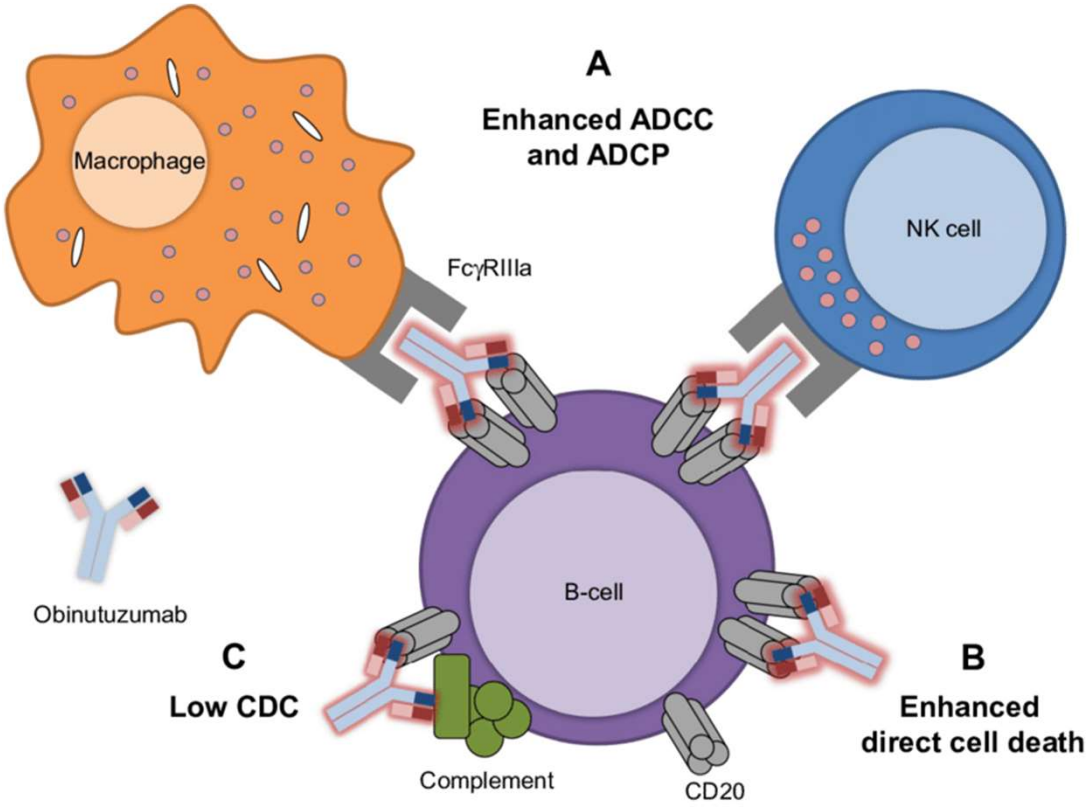
Obinutuzumab



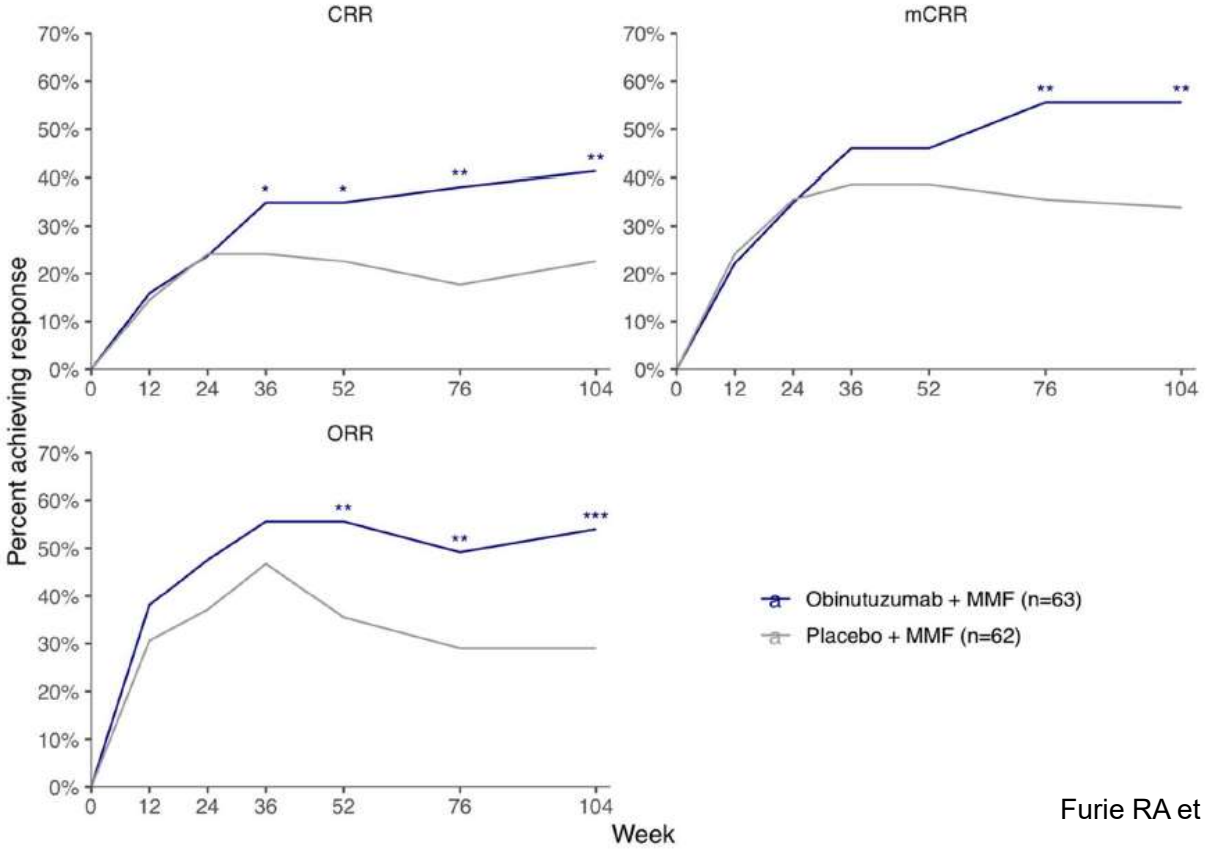
- Different CD20 epitope
- Afucosylated Fc region :
  - Better binding to FcGamma receptor
- Hinge modification
  - Enhanced direct cell death.

OPEN ACCESS

CLINICAL SCIENCE

B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial

Richard A Furie,[1] Gustavo Aroca,[2] Matthew D Cascino,[3] Jay P Garg,[3] Brad H Rovin,[4] Analia Alvarez,[5] Hilda Fragoso-Loyo,[6] Elizabeth Zuta-Santillan,[7] Thomas Schindler,[8] Paul Brunetta,[3] Cary M Looney,[3] Imran Hassan,[9] Ana Malvar[10]



Furie RA et al Ann Rheum Dis. 2022 Jan;81(1):100-107.

Obinutuzumab In Patients With Sjogren's Disease Immunized Against Rituximab

Pezot M et al 2023, in revision

Context: ADAb to rituximab

Immunization to RTX more common in systemic autoimmune diseases than in RA

	Patients tested for ADA to RTX ($n = 62$)			
	RTX-ADA Positive ($n = 14$)	RTX-ADA Negative ($n = 48$)	Univariate analysis *P*-value	Multivariate analysis *P*-value, OR [95% CI]
Age	50.5 [25-65]	61, 5 [22-85]*	$P = 0.002$	NS
Disease duration	12 [2-21]	10 [1-34]	$P = 0.45$	—
No. female patients	12 (85.7%)	40 (83.3%)	$P = 1$	—
Ethnic group				
Caucasian	6 (42.8%)	40 (83.3%)*	$P = 0.004$	—
African	8 (57.1%)	2 (4.2%) *	$P < 0, 001$	$P < 0.001$, OR=9.25 [5.08, 302.12]
Asian	0 (0%)	6 (12.5%)	$P = 0.32$	—
Disease characteristics				
RA	3 (21.4%)	32 (66.7%)*	$P = 0.004$	—
Other sAID	11 (78.6%)	16 (33.3%)*	$P = 0.004$	$P = 0.026$, OR=5.35 [1.43, 54.75]
pSS	5 (35.7%)	9 (18.8%)	$P = 0.273$	—
SLE	5 (35.7%)	4 (8.3%)*	$P = 0.02$	—

Combier et al Rheumatology 2020

Methods

- Inclusion criteria
  - Obinutuzumab treatment
  - Sjögren's Disease
  - ADAb or infusion reaction in infusions>1

- Primary endpoint
  - Physician response
  - ESSDAI response (>3 points improvement)

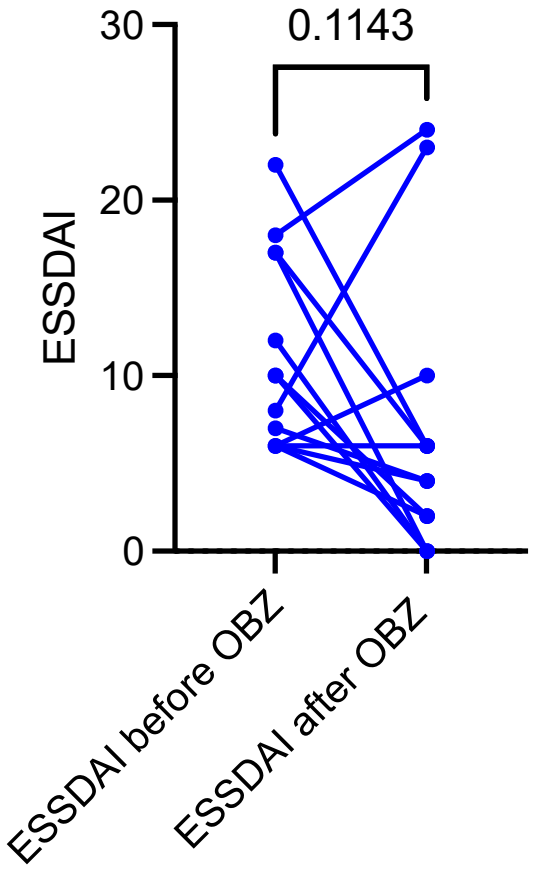
Results

- 13 Patients included
  - Reason for ADAb detection :
    - Loss of efficacy n=7
    - Infusion reaction=1
    - Both n=5
  - 11/13= 84%detectable ADAb
    - 1 not tested but infusion reaction
    - 1 Negative but no CD19 depletion after infusion
  - 8/13=61% Sjögren's disease
    - 1 Malt lymphoma
    - 1 Waldenström's lymphoma
    - 1 CLL
  - 5/13 = 32% Sjögren's disease associated with another connective tissue disease
    - 3 SLE
    - 2 Anti-synthetase

Results:

- Assessment of response at 6 months
  - 7/13=54% responded by physician evaluation
  - 8/13=62% responded by ESSDAI response (Median 10->4 p=0,11)

- Tolerance median 9 months of follow up
  - 8/13= 62% Non severe infection
  - 3/8=37,5 Benign Covid-19
  - 1/8= 12,5% Pulmonary embolism



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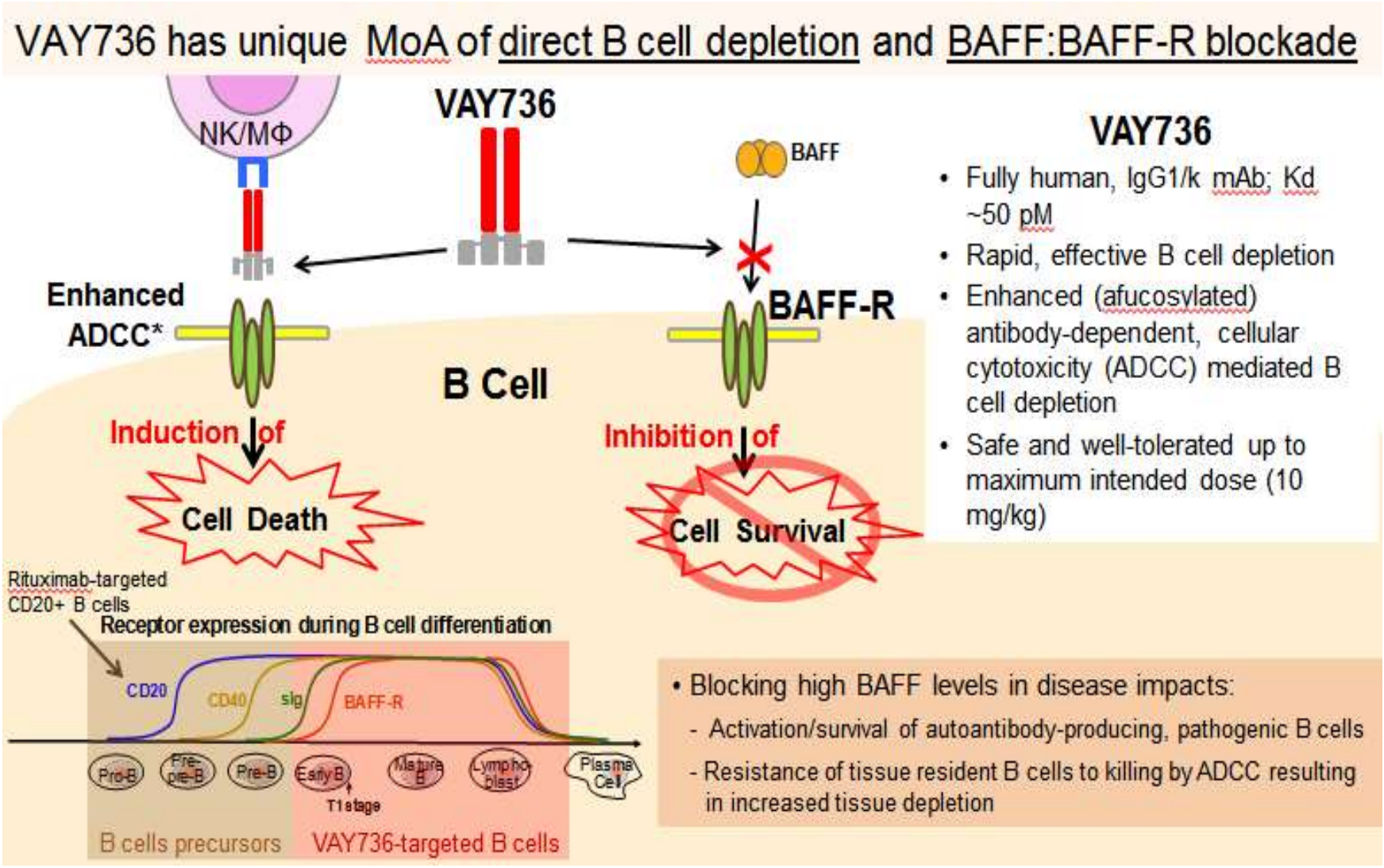
Ianalumab: an Anti-BAFF-R Ab that combines B-cell depletion and BAFF/BAFF-R inhibition

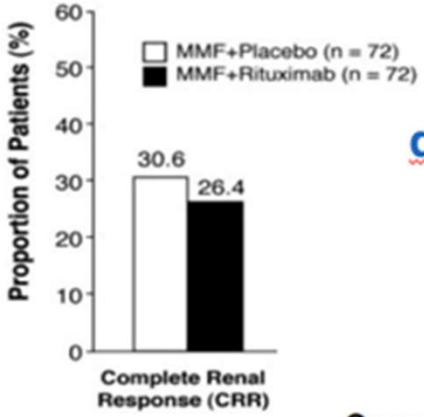


Bowman S et al. The Lancet 30 Nov 2021

VAY736 MoA1: enhanced B cell lysis

Evidence from the literature and generated in house

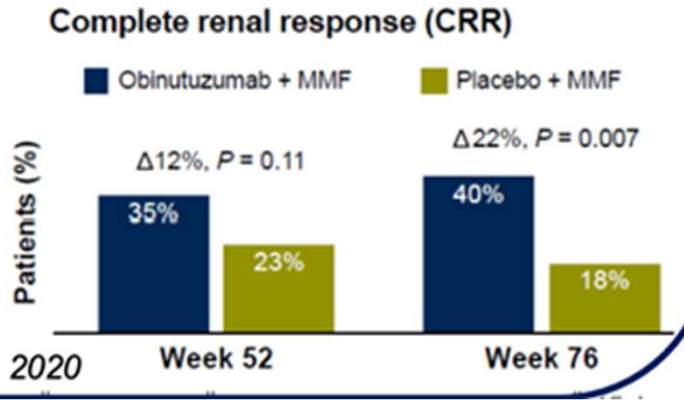
Rituximab



Rovin, 2012

Enhanced B cell depletion leads to better clinical responses in Lupus Nephritis

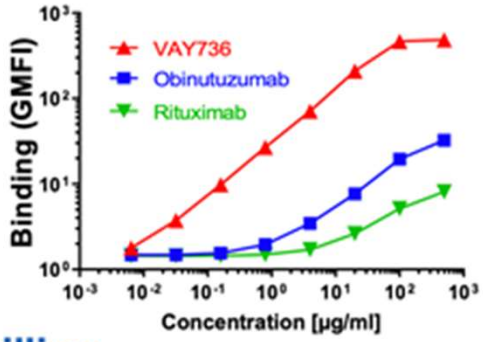
Obinutuzumab



Rovin, 2020

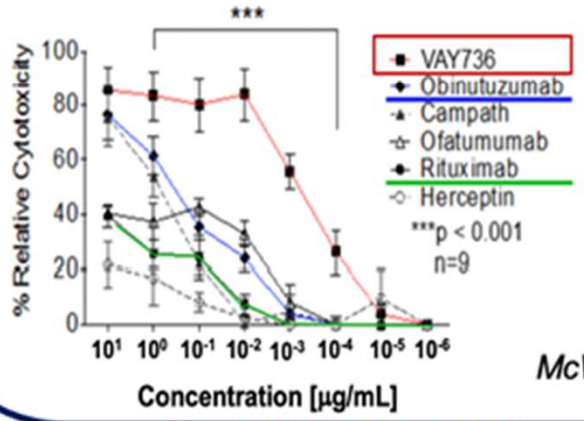
VAY736 shows superior killing due to increased recruitment of effector cells

Binding to FcγRIII



NK-dependent B cell killing

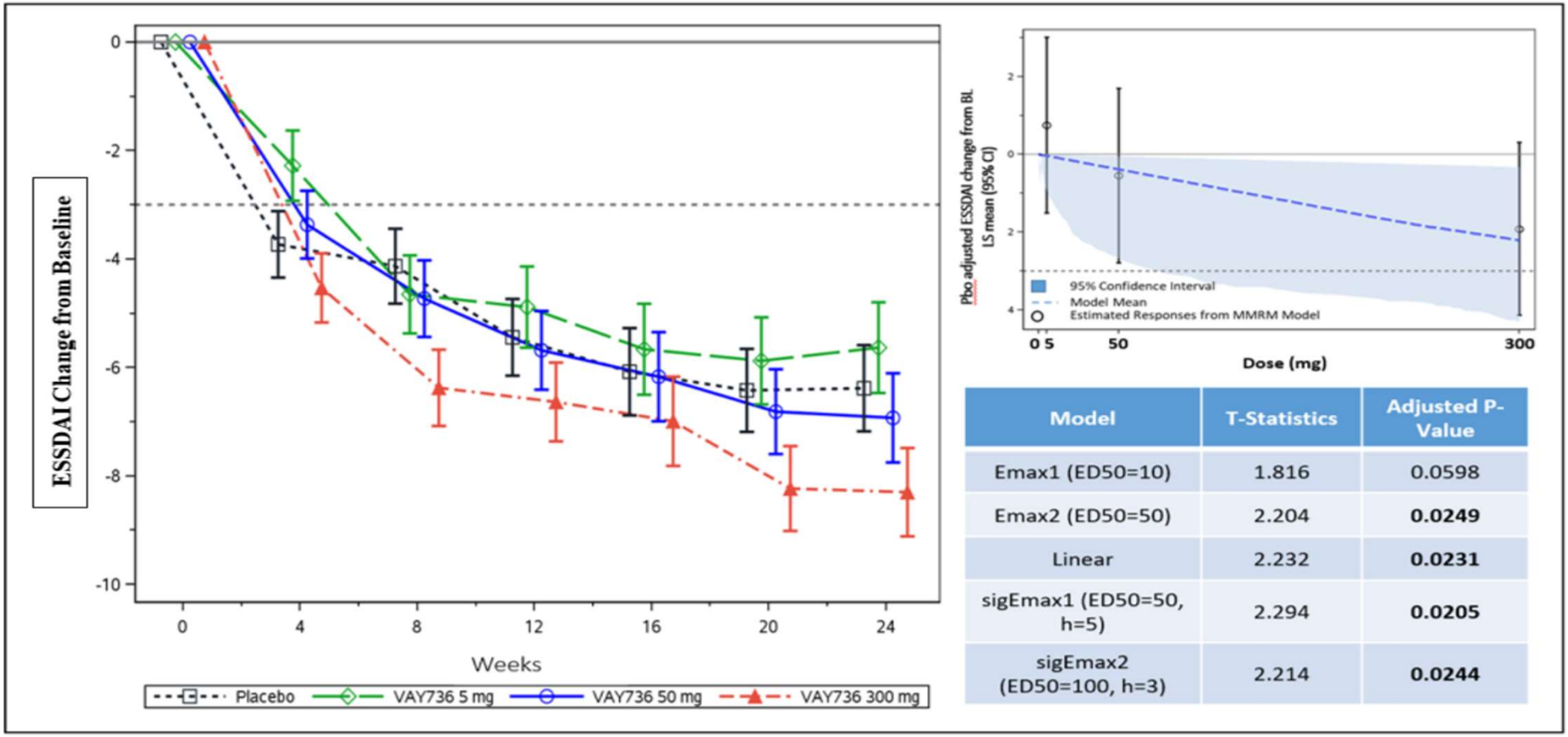
Lab Isnardi



McWilliams, 2018

NOVARTIS | Reimagining Medicine

Ianalumab in Sjögren: ESSDAI Change from Baseline over Time up to Week 24 Reveals a Statistically Significant Dose Response Relationship*



Model	T-Statistics	Adjusted P-Value
Emax1 (ED50=10)	1.816	0.0598
Emax2 (ED50=50)	2.204	**0.0249**
Linear	2.232	**0.0231**
sigEmax1 (ED50=50, h=5)	2.294	**0.0205**
sigEmax2 (ED50=100, h=3)	2.214	**0.0244**

*The simulated dose response is based on model average method through bootstrapping technique.
ESSDAI, EULAR Sjogren's Syndrome Disease Activity

Bowman S et al. The Lancet 30 Nov 2021

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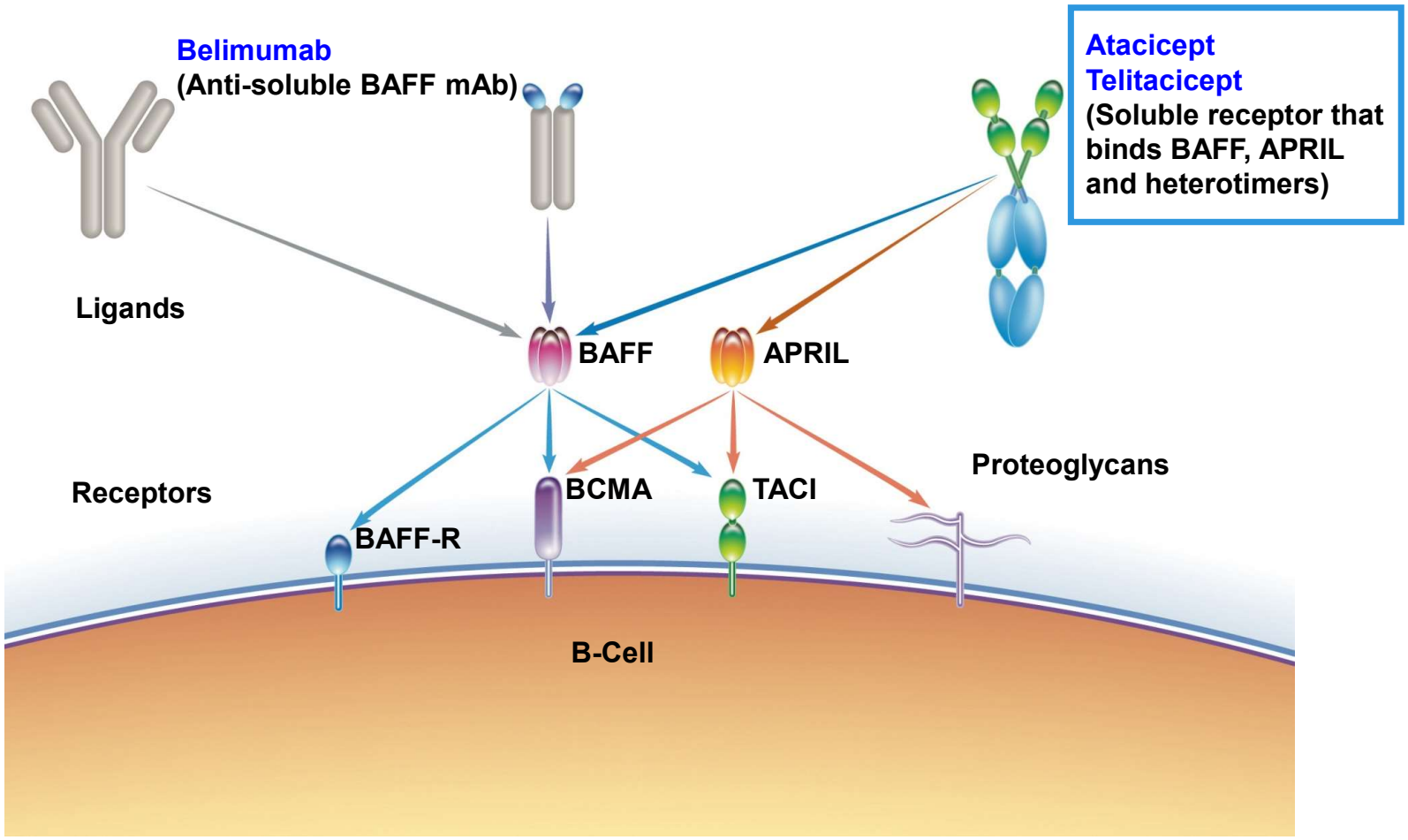
Perspectives for targeting plasmablasts and plasma cells

- TACI-Fc: Inhibitor of BAFF and APRIL
  - Atacicept
  - Telitacicept

- All new drugs that work in multiple myeloma
  - Bortezomib and other proteasome inhibitors
  - Daratumumab: anti-CD38 Ab
  - Anti-BCMA Ab
  - Anti-BCMA / CD3 bispecific Ab

Targeting plasma cells by inhibiting BAFF + APRIL

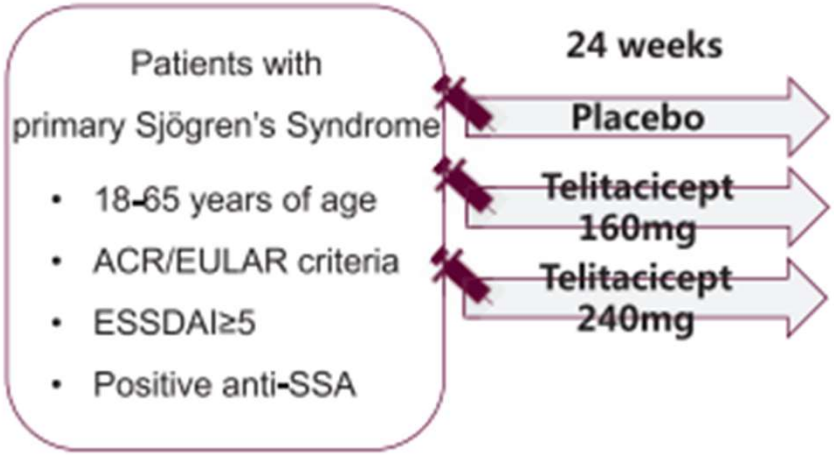


Clinical science

Rheumatology, July 2023

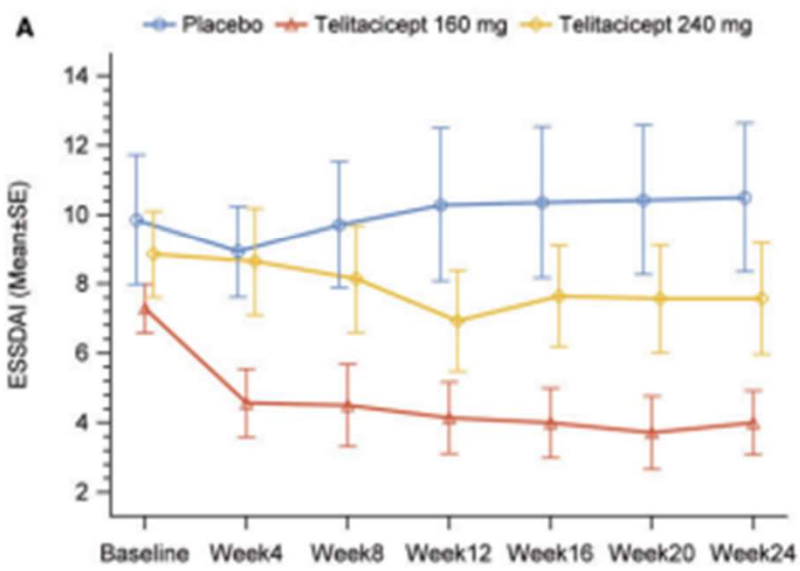
Efficacy and safety of telitacicept in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled, phase 2 trial

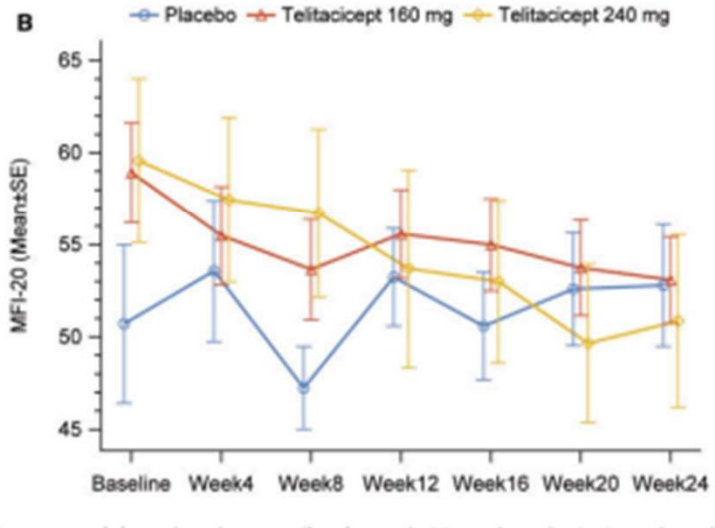
Dong Xu [1,†], Jianmin Fang[2,†], Shangzhu Zhang[1], Cibo Huang[3], Chenghui Huang[4], Li Qin[5], Xiaom
Meiqing Chen[7], Xiumei Liu[8], Yi Liu[9], Zhijun Li[10], Jiankang Hu[11], Chunde Bao[12], Wei Wei [13],
Jing Tian[14], Xinwang Duan[15], Xiaofeng Zeng [1,*]



Changes (Mean±SD)	Placebo (n=14)	Telitacicept 160mg/week (n=14)	Telitacicept 240mg/week (n=14)
ESSDAI	0.6±4.55	-3.3±2.73 *	-1.3±4.14
MFI-20	7.0±9.35	-4.0±10.3 *	-5.1±8.94 *
Serious Adverse Events, n(%)	1(7.14%)	0(%)	0(%)

*: when compared with placebo, p<0.05





nature medicine

Article

https://doi.org/10.1038/s41591-023-02479-1

Daratumumab monotherapy for refractory lupus nephritis

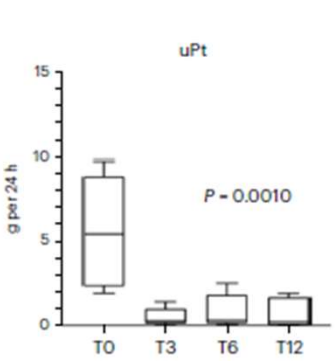
Received: 12 January 2023

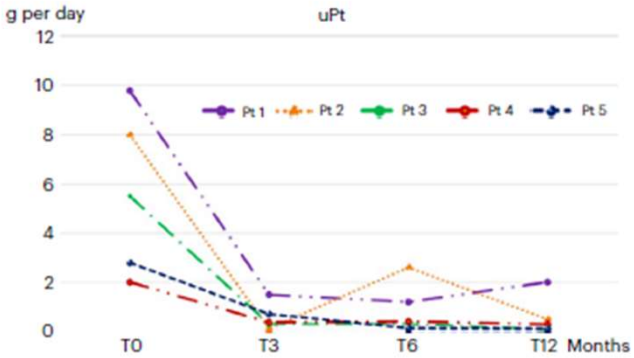
Accepted: 29 June 2023

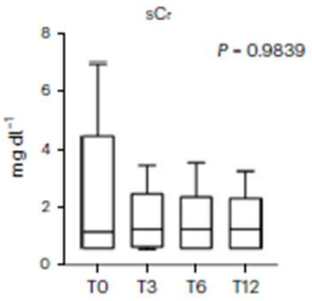
Published online: 10 August 2023

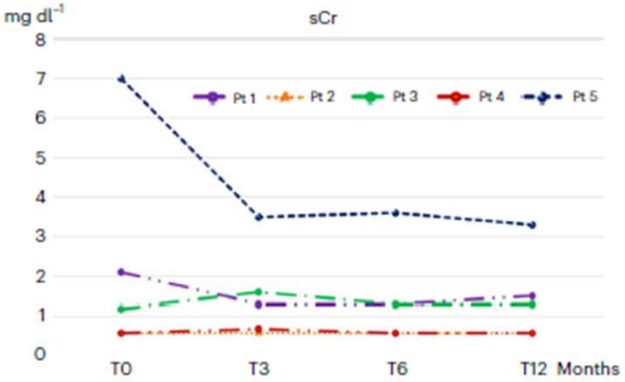
Dario Roccatello[1,2] ✉, Roberta Fenoglio[1,2], Ilaria Caniggia[1], Joelle Kamgaing[1], Carla Naretto[1], Irene Cecchi[1], Elena Rubini[1], Daniela Rossi[1], Emanuele De Simone[1], Giulio Del Vecchio[1], Martina Cozzi[1] & Savino Sciascia[1]

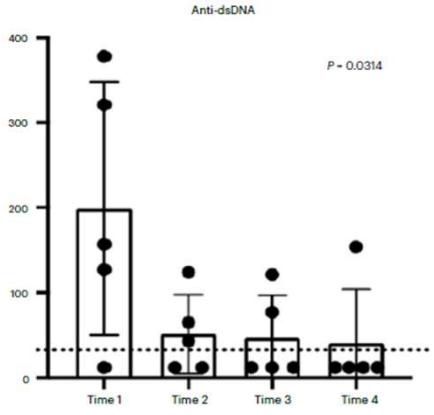
- 6 patients with refractory lupus nephritis
- Daratumumab 16 mg kg^{-1} weekly IV for 8 weeks and then every 2 weeks for 8 more times and then monthly for another eight times. 125 mg IV methylprednisolone before each infusion.
- 5/6 patients responders











Roccatello D et al. Nat Med. 2023 Aug;29(8):2041-2047..

Sjögren syndrome

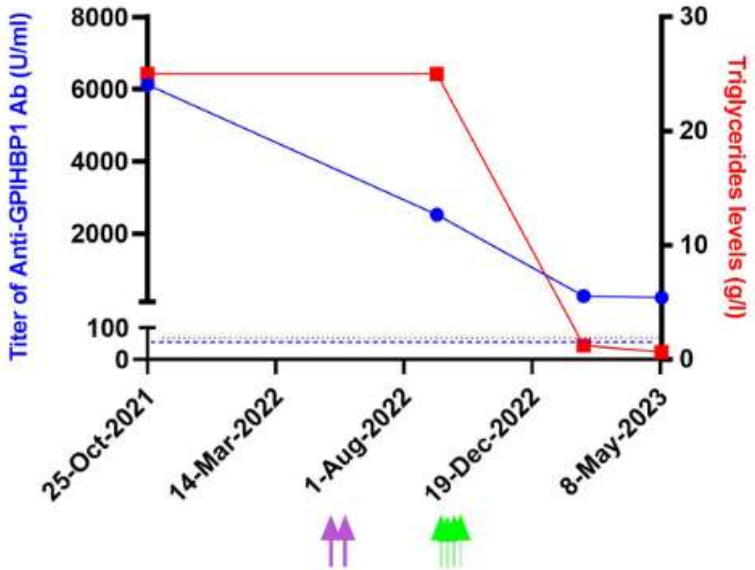
RMD Open
Rheumatic & Musculoskeletal Diseases

LETTER

Efficacy of daratumumab in refractory primary Sjögren disease

Gaetane Nocturne [1,2] Oriane Marmontel,[3,4] Mathilde di Filippo,[3,4] Pascale Chretien,[5] Roman Krzysiek,[5] Francois Lifermann,[6] Nawal Rahal,[1] Rakiba Belkhir,[1] Philippe Moulin,[3,4] Xavier Mariette [1,2]

- 1 patient with SjD with huge hyper triglyceridemia due to anti-glycosylphosphatidylinositol-anchored high- density lipoprotein binding protein1 (GPIHBP1)
- 1 patient with refractory cryo-associated vasculitis
- Only 1 cycle of daratumumab 1800 mg subcutaneously once a week for 4 weeks



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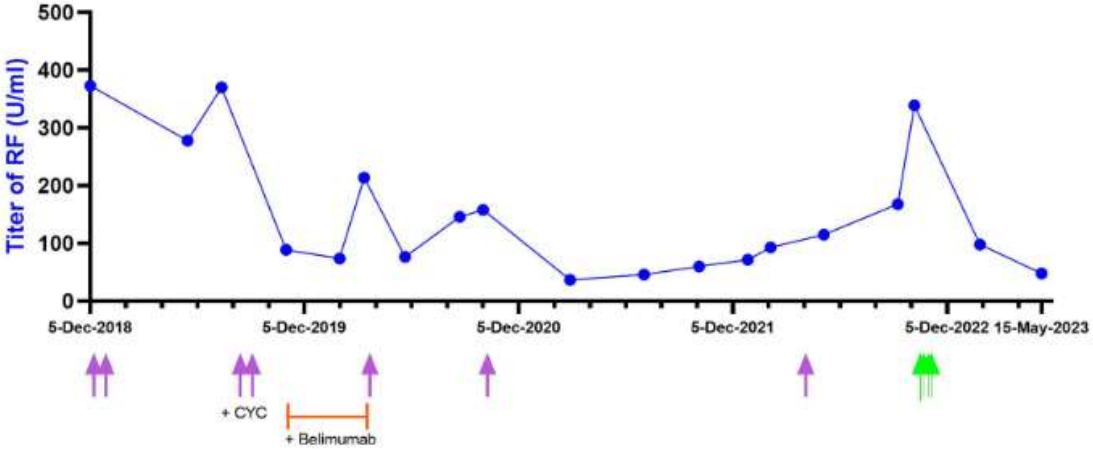

Nocturne G et al. RMD Open 2023;9:e003464.

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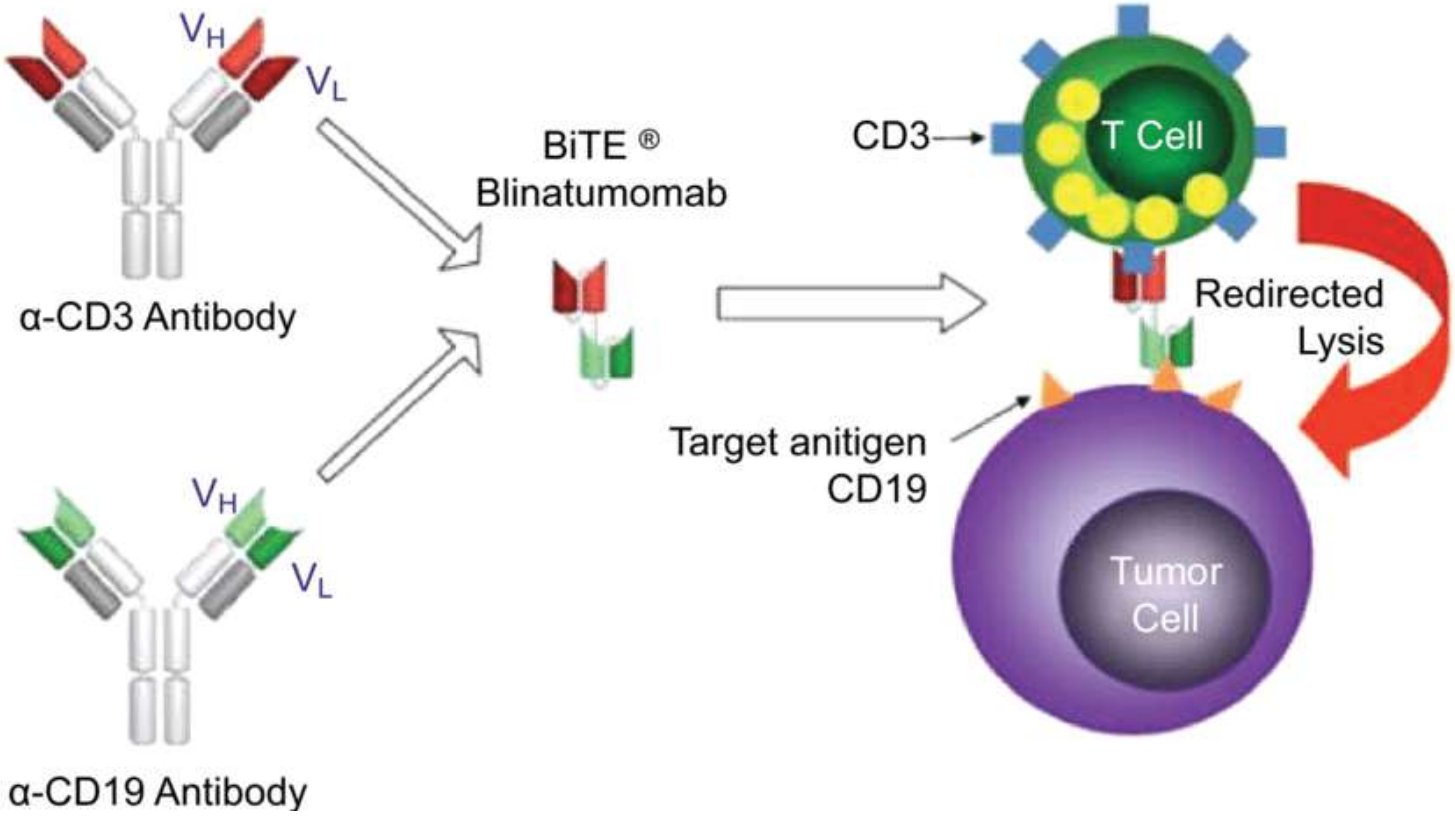
  - In autoimmune diseases

Historique des bispécifiques dans les hémopathies

Blinatumomab (BiTE anti CD19 – anti CD3) dans les **LAL phi neg en rechute ou réfractaire**
FDA 2014, EMA 2015, AMM en 2018.
« pont vers l'allogreffe ou CART »



Research gate

Développement ultérieur des bispécifiques anti CD20/CD3 dans le lymphome

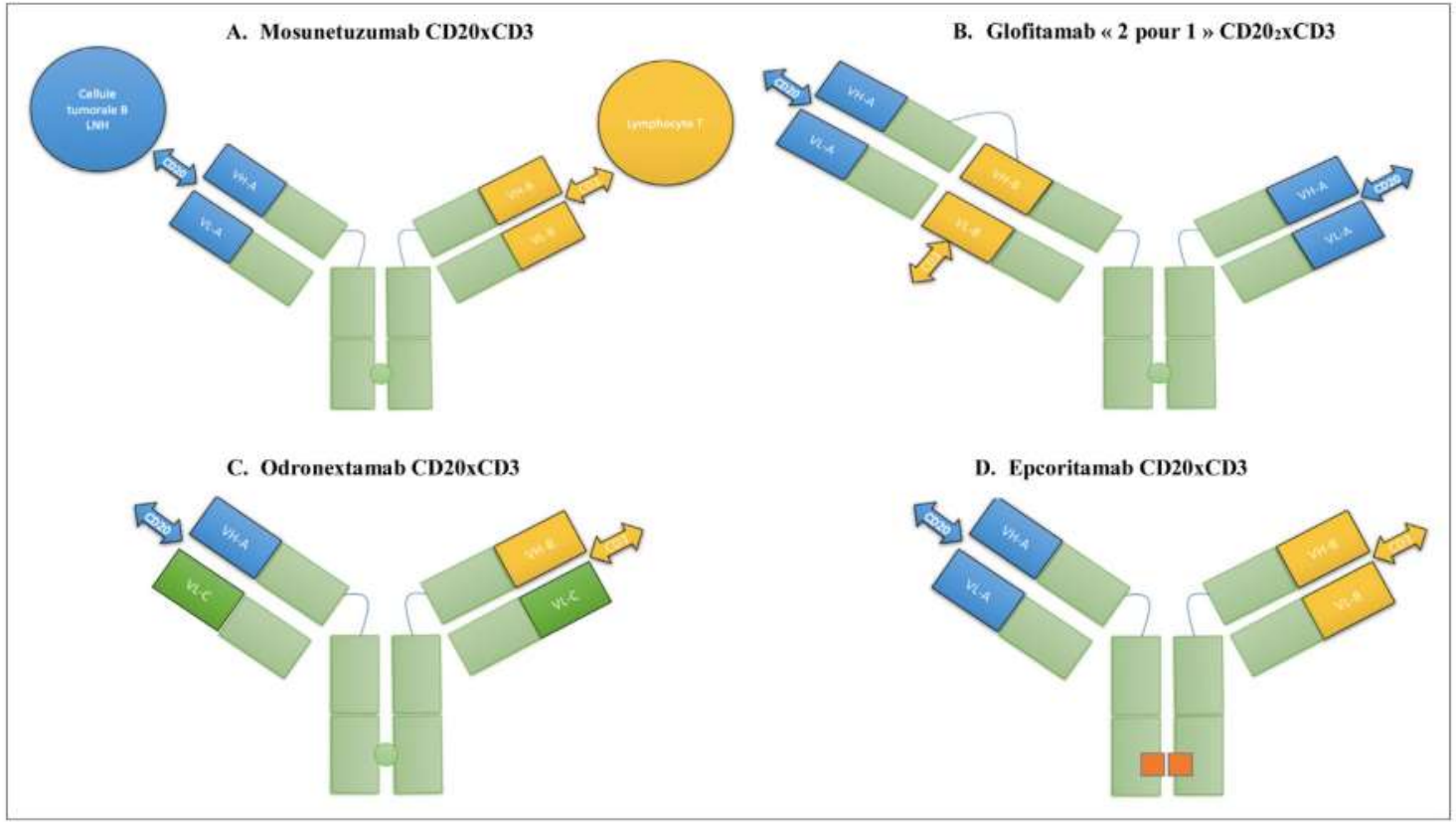


FIGURE 2

Anticorps bispécifiques dans les lymphomes non hodgkinien : construction avec une région Fc

A : mosunetuzumab CD20 × CD

B : glofitamab « 2 pour 1 » $CD20_2$ × CD3

Bull Cancer 2021; 108: S195-S204

TABLEAU I

Domaines d'application des anticorps bispécifiques

Hémopathie	Molécule	Structure et cibles	Phase	Réponse	Administration
LNH	Mosunetuzumab	CD20 × CD3 BiTE	Phase I/Ib 270 pts	RG 63 % indolent RG 37 % agressif	Tous les 21 j IV
	Glofitamab	$CD20_2$ × CD3 BiTE	Phase II 52 pts	RG 66,7 % indolent RG 60,7 % agressif	Tous les 21 j IV
	Odronextamab	CD20 × CD3 BiTE	Phase I 127 pts	RG 93 % indolent RG 55 % agressif	Hebdo × 12 (3 M) puis tous les 15 j IV
	Epcoritamab	CD20 × CD3 BiTE	Phase I/II 26 pts	RG 100 % indolent RG 67 % agressif	Tous les 28 j SC
LH	AFM13	CD30 × CD16a BiKE	Phase II 25 pts	RG 17 %	Hebdo IV

Bull Cancer 2021; 108: S195-S204

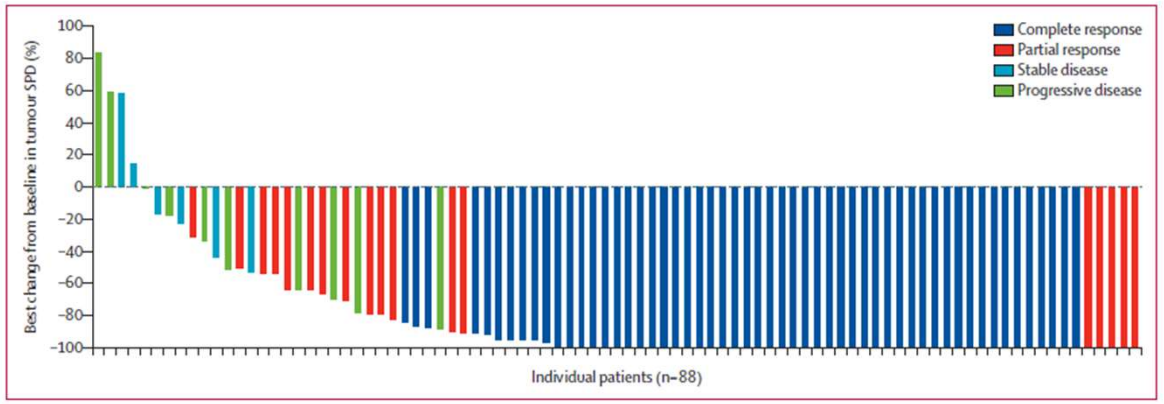
Développement dans les **lymphomes B diffus grandes cellules** :
. Epcoritamab en association à RCHOP en première ligne DLBCL, phase III
. Chez des patients fragiles, contre indiqués aux anthracyclines

Développement dans les **lymphomes folliculaires** :
. Epcoritamab en association à Rituximab Revlimid LF R/R, phase III

Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study

Lihua E Budde, Laurie H Sehn, Matthew Matasar, Stephen J Schuster, Sarit Assouline, Pratyush Giri, John Kuruvilla, Miguel Canales, Sascha Dietrich, Keith Fay, Matthew Ku, Loretta Nastoupil, Chan Yoon Cheah, Michael C Wei, Shen Yin, Chi-Chung Li, Huang Huang, Antonia Kwan, Elicia Penuel, Nancy L Bartlett

Mosunetuzumab: Bispécific anti-CD3/CD20



- 80% reponders
- 60% complete response
- Median PFS: 17,9 months

90 refractory patients

Number of previous lines of therapy	3 (2–4)
Two previous lines	34 (38%)
Three previous lines	28 (31%)
More than three previous lines	28 (31%)
Previous lymphoma therapy	
Alkylator therapy	90 (100%)
Anti-CD20 therapy	90 (100%)
Immunochemotherapy (anti-CD20 plus alkylator or anthracycline)	88 (98%)
Anthracyclines	74 (82%)

Safety

	Grade 1–2	Grade 3	Grade 4
Cytokine release syndrome	38 (42%)	1 (1%)	1 (1%)
Fatigue	33 (37%)	0	0
Headache	27 (30%)	1 (1%)	0
Neutropenia or decreased neutrophil count	2 (2%)	12 (13%)	12 (13%)
Pyrexia	25 (28%)	1 (1%)	0
Hypophosphataemia	9 (10%)	15 (17%)	0
Pruritus	19 (21%)	0	0

Budde LE. Lancet Oncol 2022; 23: 1055–65

Anti-BCMA/CD3 Antibodies in multiple myeloma

Table 1. Phase 1 and 2 studies evaluating the safety and efficacy of bispecific antibodies targeting BCMA, GPRC5D, and FcRH5 in multiple myeloma.

BiAB, Trial	Targets	BiAB Structure	N	Design	ORR, CR (%)	CRS (All Grade, ≥Grade 3) %	ICANS (%)	Infections (%)
Teclistamab (Ph1-2, NCT04557098) [32]	BCMAxCD3	Humanized IgG Fc	165	SQ, weekly injection at dose of 1.5 mg/kg. Step-up doses of 0.06 mg and 0.3 mg per kilogram.	63.0, 39.4	72.1, 0.6	3.0	76.4
Elranatamab (Ph2, NCT04649359) [33]	BCMAxCD3	Humanized IgG2a	123	SQ, weekly injection at a dose of 76 mg for a 28-day cycle. Two step-up doses at 12 mg and 32 mg.	61.0, 27.6	56.3, 0.0	3.4	61.8
Linvoseltamab (Ph2, NCT03761108) [34]	BCMAxCD3	Fc Fab arms	252	Two cohorts received doses of 50 mg and 200 mg, respectively. IV, with two step-up doses. A protocol amendment allowed pts who progressed at 50 mg to dose escalate to 200 mg.	50 mg cohort: 50.0, 20.2 200 mg cohort: 64.0, 24.1	50 mg cohort: 53.0, 1.0 200 mg cohort: 37.0, 2.0	Grade 3 or 4 50 mg cohort: 1.0 200 mg cohort: 2.0	50 mg cohort: 59.0 200 mg cohort: 43.0
Abbv-383 (Ph1, NCT03933735) [35]	BCMAxCD3	IgG4 Fc	124	IV, once every 3 weeks. Doses of 40 mg and 60 mg for escalation and expansion cohorts.	57.0, 29.0	40 mg cohort: 83.0, 0.0 60 mg cohort: 72.0, 2.0	NR	40 mg cohort: 50.0 60 mg cohort: 43.0
Talquetamab (Ph1, NCT03399799) [36]	GPRC5DxCD3	Humanized IgG4	232	102 patients IV weekly or every other week at doses from 0.5 to 180 µg per kilogram of body weight. 130 patients SQ weekly, every other week, or monthly at doses from 5 to 1600 µg per kilogram.	At SQ doses of 405 µg/kg: 70.0, 23.0 and 800 µg/kg: 64.0, 23.0	At SQ doses of 405 µg/kg: 77.0, 3.0 and 800 µg/kg: 80.0, 0.0 At IV doses: 49.0, 5.0	NR	NR
Cevostamab (Ph1, NCT03275103) [41]	FcRH5xCD3	Humanized IgG1	160	IV administration in 21-day cycles. Two step-up doses.	At 160 mg dose: 54% At 90 mg dose: 36.7	80.0, 1.3	NR	42.5, 18.8

BiAb = bispecific antibody. CRS = cytokine release syndrome. ICANS = immune effector cell-associated neurotoxicity syndrome. ORR = overall response rate. CR = complete response. NR = not reported. SQ = subcutaneous. IV = intravenous.

Outline

- Improving B-cell depletion induced by rituximab
  - Rituximab + Belimumab
  - Obinutuzumab
  - Ianalumab
- Targeting plasma cells:
  - Daratumumab
- **Bispecific antibodies**
  - In hematology
  - **In autoimmune diseases**

Chimeric autoantigen-T cell receptor (CATCR)-T cell therapies to selectively target autoreactive B cells

Maximilian F. Konig, M.D. ACR 2022

Les CAR-T cells *(chimeric antigen receptor)* ciblant les B

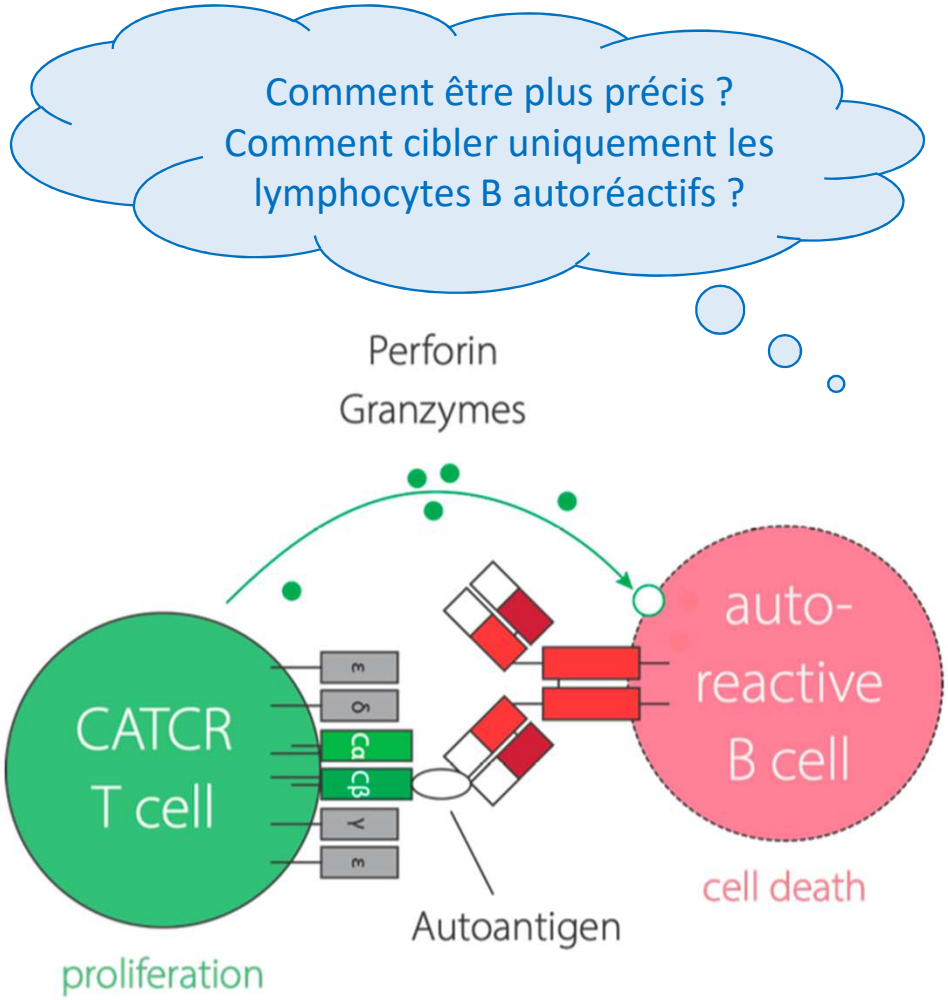
- Les CAR-T cells ciblant le CD19 sont efficaces dans plusieurs hémopathies B
- Ces traitements pourraient-ils induire des rémissions durables dans le lupus

Chimeric autoantigen-T cell receptor (CATCR)-T cells

Les CATCR sont des récepteurs des T dans lesquels un autoantigène a été introduit dans une ou plusieurs protéines du complexe TCR-CD3, conférant ainsi à ces CATCR-T cells une spécificité antigénique contre un autoantigène identifié :

→ Plus spécifique mais dirigé contre un seul autoantigène

→ Moins déplétant vis-à-vis des autres lymphocytes B, et donc potentiellement mieux toléré

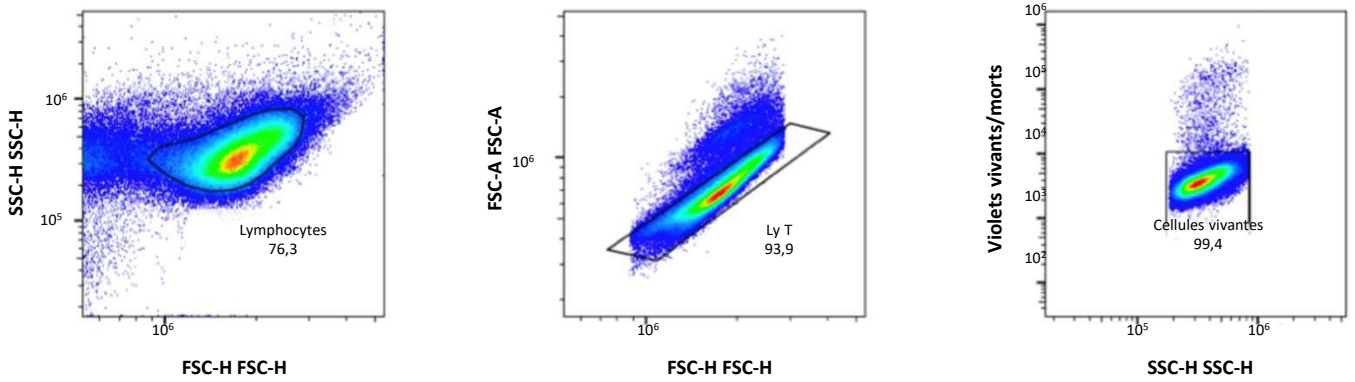


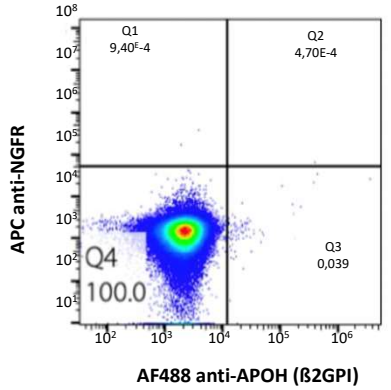
Modèle de CATCR-T cells pour le SAPL

Construction du β2GP1-CATCR-T cell

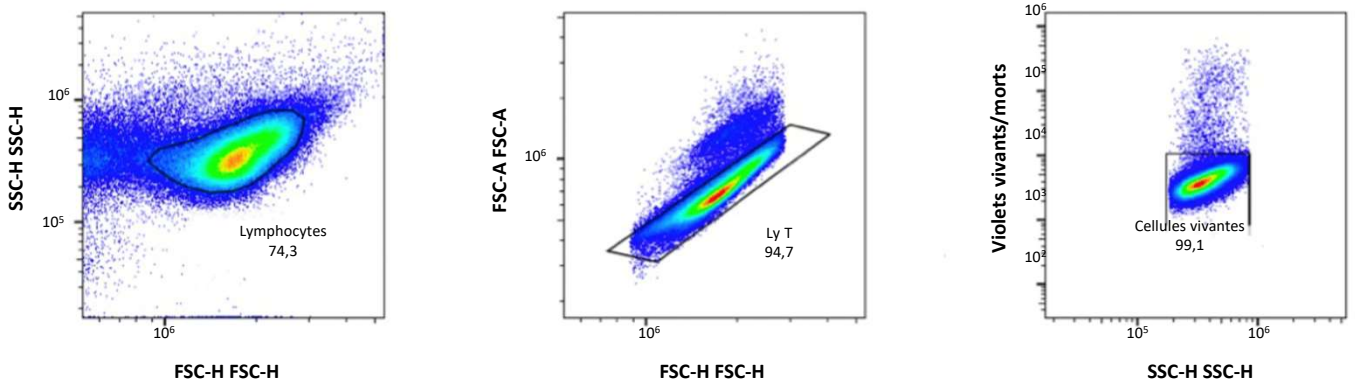
→ Incorporation de l'autoantigène β2GP1 dans le complexe TCR-CD3 de cellules T humaines par **CRISPR-Cas9/12a**

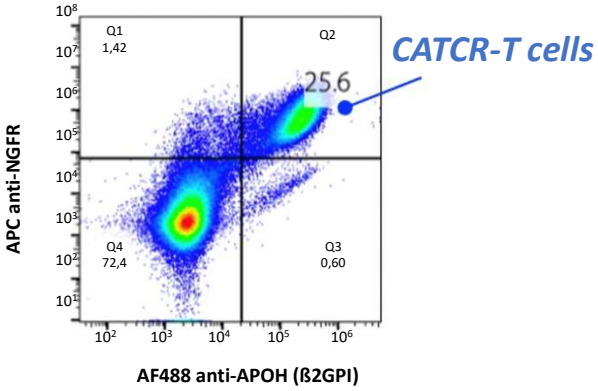
LT sans insertion du CATCR





β2GP1-CATCR-T cell

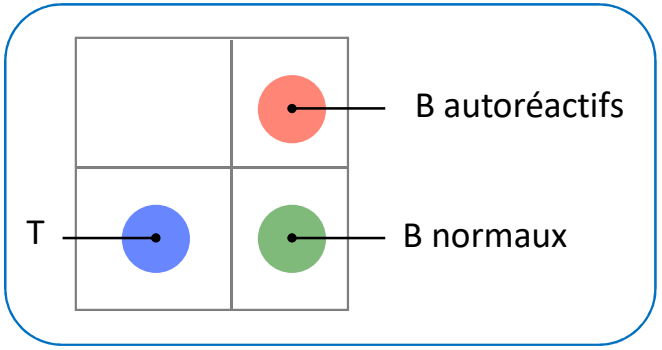




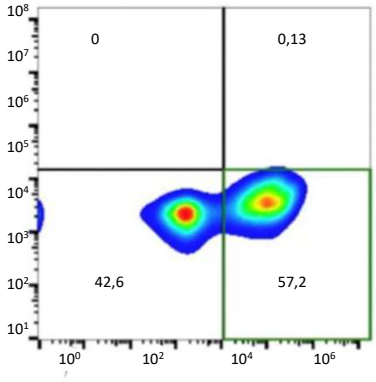
→ Les CATCR-T cells tuent sélectivement les B autoréactifs

Mise en coculture de lymphocytes T normaux ou CATCR-T cells, avec des lymphocytes B normaux ou rendus autoréactifs par une modification de leur BCR par CRISP-Cas9

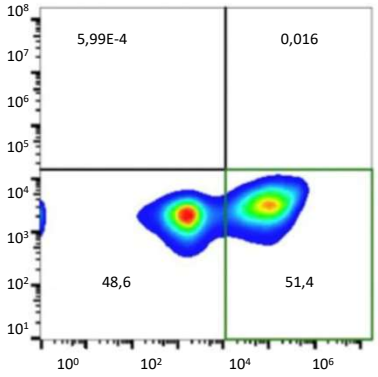
→ Mesure de la cytotoxicité par cytométrie de flux



T non modifié vs
B non modifiés

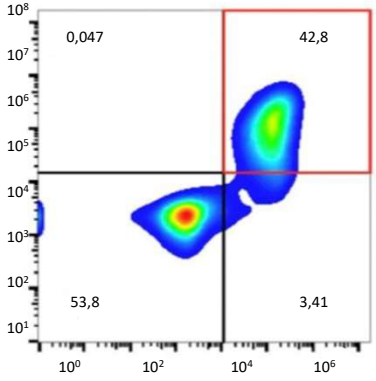


CATCR-T cells vs
B non modifiés

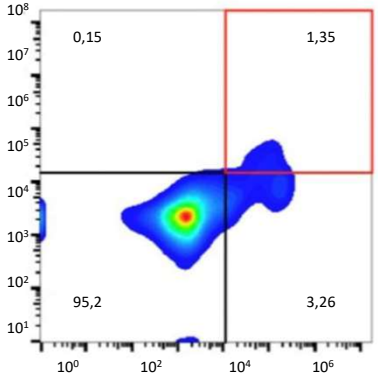


CATCR-T ne détruit pas les B normaux

T non modifié vs
B modifiés anti-β2GPI



CATCR-T cells vs
B modifiés anti-β2GPI



CATCR-T détruit les B anti-β2GPI autoréactifs

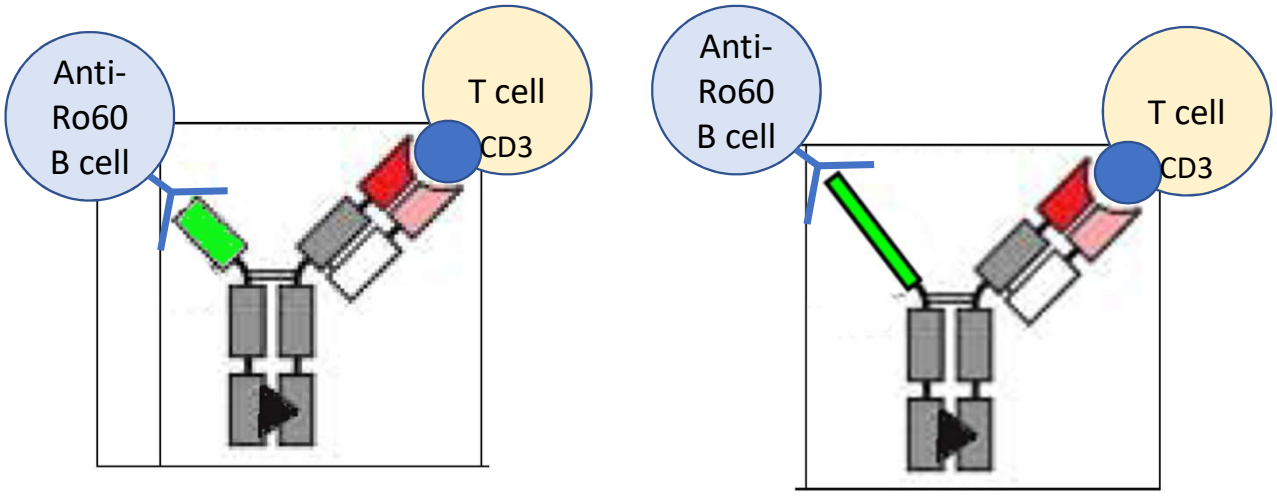
DL488 anti-β2GPI BCR

APC anti-CD19

ect: to deplete autoimmune B cells in Sjögren's disease with antigen Ro60/anti-CD3 bispecific antibody (ATBis)

- Mouse model of Sjögren by immunization with the 273-289 peptide of Ro60 (peptide identical in mouse and human Ro60)
  - → Development of Sjögren like disease with anti-Ro60 Ab, decrease of salivary flow and salivary gland lymphocytic infiltration

- Treatment of these mice with
  - Anti-CD20 Ab
  - Anti-CD3/CD20 Bispecific Ab
  - Anti-CD3/Ro60 Autoantigen/T-cell Bispecific Ab (ATBis)



S Bitoun, B Maillere, X Mariette, in preparation

Take home messages

- CAR-T cells targeting CD19 are efficient but large scale dissemination will be difficult even if it will became simpler
- Their mechanism of action is just a profound B-cell depletion and thereafter a reset of the immune system
- Profound B-cell depletion can be achieved by other simpler methods
  - New anti-CD20
  - Combination of anti-CD20 and anti-BAFF
  - Anti-BAFF-R
  - Bispecific antibodies
- Depletion of plasma cells has also to considered in lupus and Sjogren
- Depletion of only the autoimmune B cells is a dream
  - CATCR T cell therapy
  - Autoantigen/T-cell Bispecific Ab (ATBis)

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  - ANR 2010-2014
  - Société Française de Rhumatologie
  - Arthritis foundation
  - PHRC 2006, 2007, 2010
  - Human Genome Science
  - Biogen
  - Fondation pour la Recherche Médicale
  - IMI-2 European commission

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