Cibler les lymphocytes B pour traiter (guérir ?) la maladie de Sjögren

Divi CORNEC

Brest

Disclosures

- No personal financial disclosures
- Research grants from Novartis, GSK, Servier, BMS, Roche-Chugai, CSL Behring, Astra-Zeneca
- Investigator for multiple clinical trials (in the domain of vasculitis: Novartis, Roche-Chugai, Eli-Lilly, Abbvie, Amgen/Chemocentryx, InflarX…)

Agenda

- Pourquoi cibler les LB ?

- Comment cibler les LB ?
  - En les détruisant ? *Déplétion, faut-il aller plus profond ?*
  - En les modulant ? *Cibler la coactivation/la signalisation des LB*
  - En éliminant les anticorps ? *Et notamment les autoanticorps*
  - En détruisant seulement les méchants ? *Le phantasme des thérapies ciblant les clones auto-réactifs*

- Où cibler les LB en France ?
  - La création du C3I

Agenda

- Pourquoi cibler les LB ?

- Comment cibler les LB ?
  - En les détruisant ? *Déplétion, faut-il aller plus profond ?*
  - En les modulant ? *Cibler la coactivation*
  - En éliminant les anticorps ? *Et notamment les autoanticorps*
  - En détruisant seulement les méchants ? *Le phantasme des thérapies ciblant les clones auto-réactifs*

- Où cibler les LB en France ?
  - La création du C3I

Rituximab

- Maladies autoimmunes (PR) = facteur de risque de lymphome

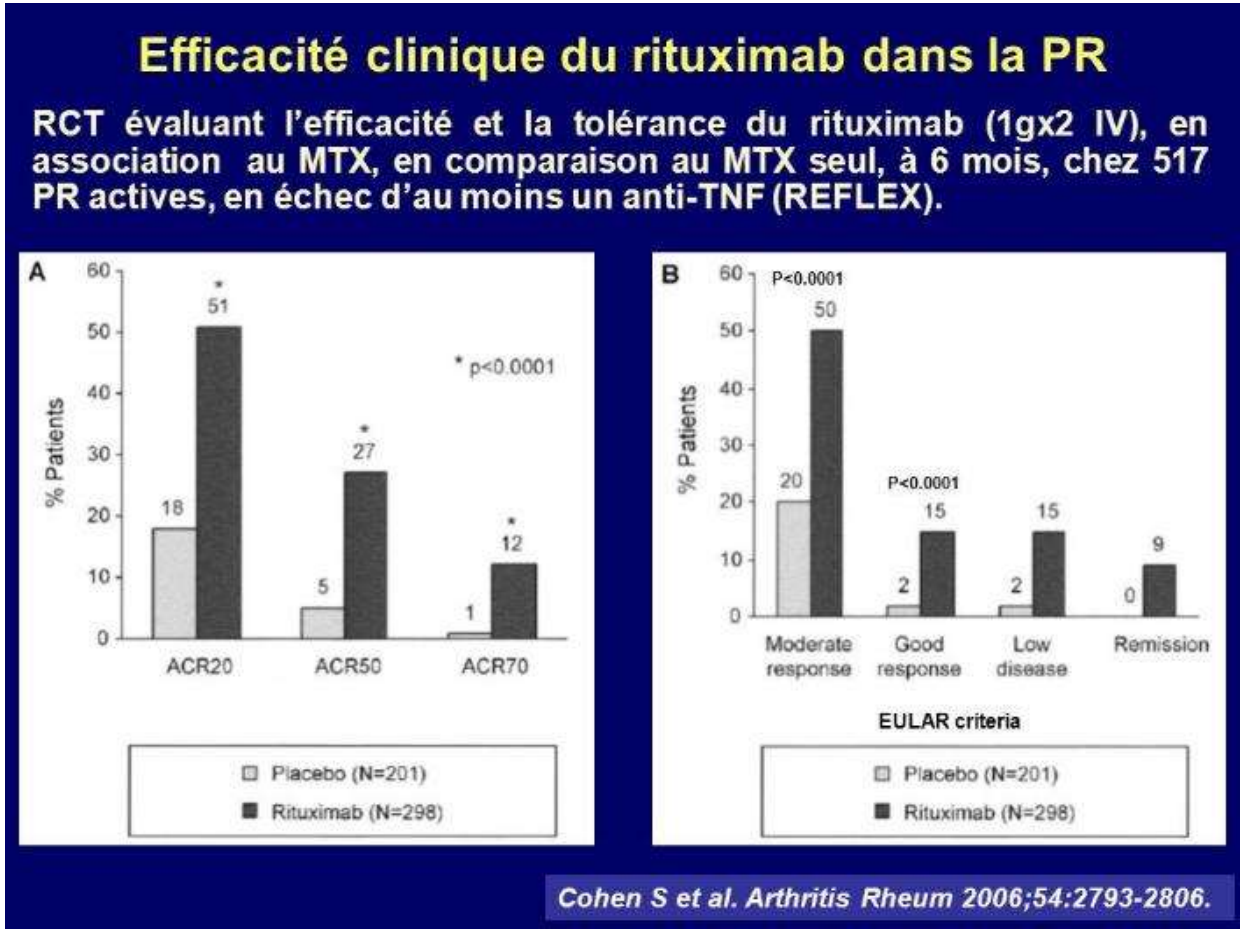
Ann Rheum Dis 2001;**60**:892–893

Lymphoma in a patient with rheumatoid arthritis receiving methotrexate treatment: successful treatment with rituximab

M Stewart, V Malkovska, J Krishnan, L Lessin, W Barth

The sustained remission of our patient's RA for more than two years after the use of rituximab was surprising but has now been described in five other patients.[18] The mechanism is unknown but may be due to the profound B lymphocyte depletion that occurs.

Rituximab


Efficacité clinique du rituximab dans la PR
RCT évaluant l'efficacité et la tolérance du rituximab (1gx2 IV), en association au MTX, en comparaison au MTX seul, à 6 mois, chez 517 PR actives, en échec d'au moins un anti-TNF (REFLEX).
A
% Patients
60
50
40
30
20
10
0
18
51
5
27
1
12
* p<0.0001
ACR20
ACR50
ACR70
Placebo (N=201)
Rituximab (N=298)
B
% Patients
P<0.0001
50
20
P<0.0001
15
2
15
2
9
0
Moderate response
Good response
Low disease
Remission
EULAR criteria
Placebo (N=201)
Rituximab (N=298)
Cohen S et al. Arthritis Rheum 2006;54:2793-2806.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 15, 2010 VOL. 363 NO. 3

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., and Ulrich Specks, M.D., for the RAVE–ITN Research Group*

Etude RAVE

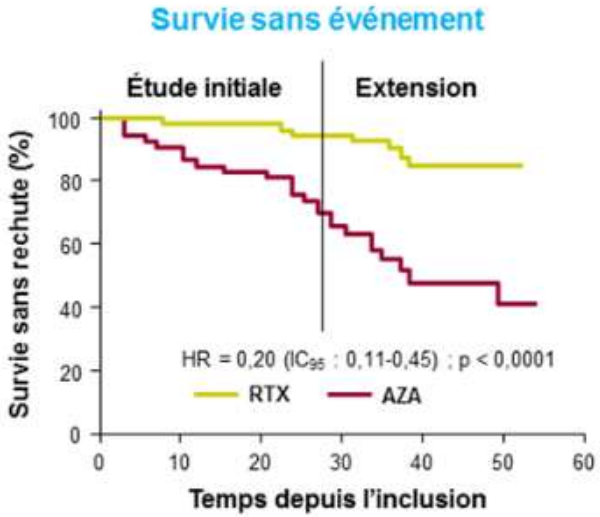
Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

Rachel B. Jones, M.R.C.P., M.D., Jan Willem Cohen Tervaert, M.D., Ph.D., Thomas Hauser, M.D., Raashid Luqmani, D.M., F.R.C.P., F.R.C.P.(E.), Matthew D. Morgan, M.R.C.P., Ph.D., Chen Au Peh, F.R.A.C.P., Ph.D., Caroline O. Savage, Ph.D., F.R.C.P., F.Med.Sci., Mårten Segelmark, M.D., Ph.D., Vladimir Tesar, M.D., Ph.D., Pieter van Paassen, M.D., Ph.D., Dorothy Walsh, B.S.C.N., Michael Walsh, M.D., F.R.C.P.(C.), Kerstin Westman, M.D., Ph.D., and David R.W. Jayne, M.D., F.R.C.P., for the European Vasculitis Study Group

Etude RITUXVAS

Etude Mainritsan : Rituximab vs Azathioprine en traitement d'entretien

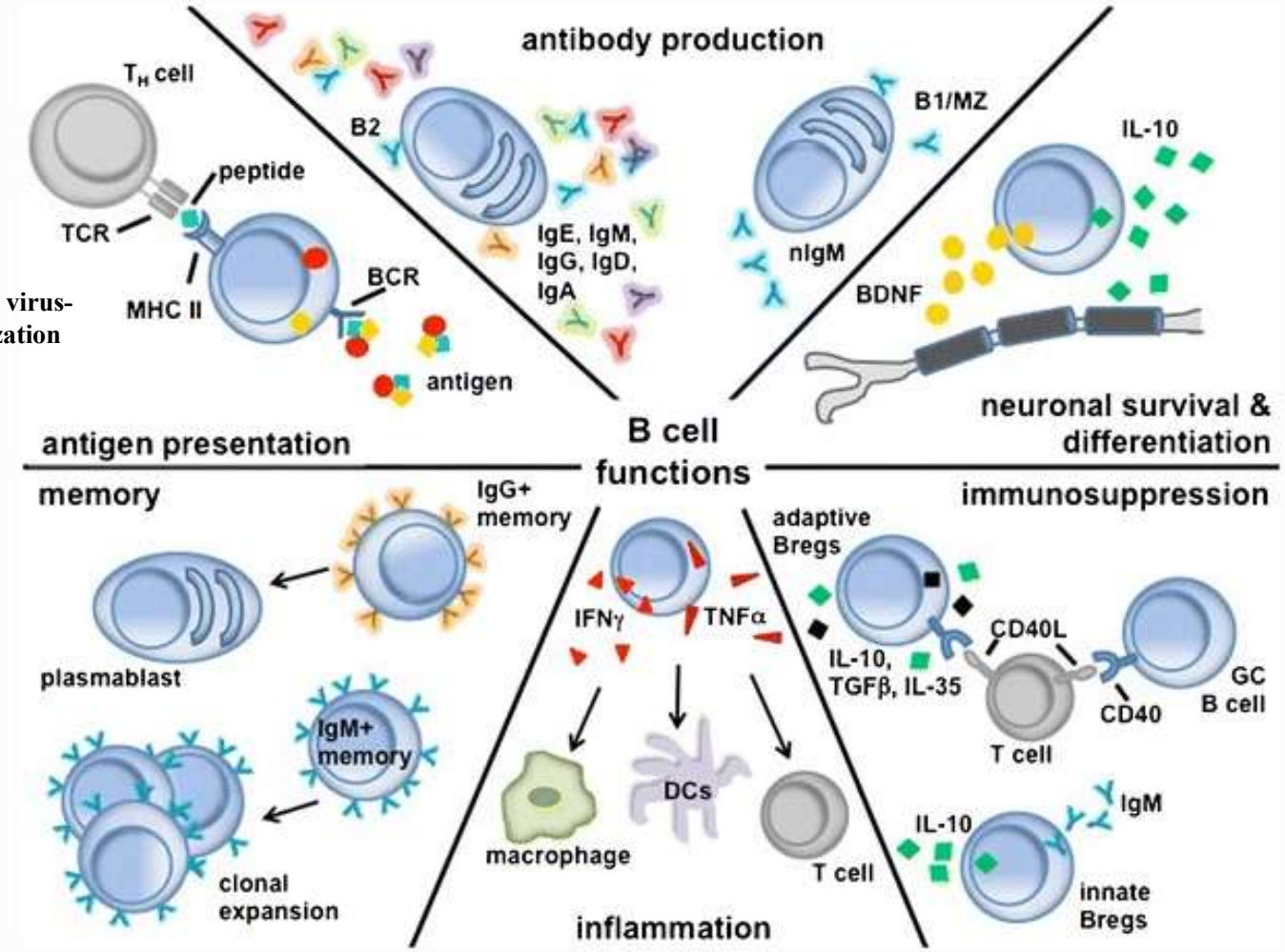
- **Résultats**
  - Durée moyenne de suivi : 38,6 mois [33,5-45,2]
  - AZA : 26/54 rechutes majeures (48,1 %)
  - RTX : 7/55 rechutes majeures (12,7 %)
- **Tolérance**
  - Décès : 3/54 groupe AZA versus 0/55 groupe RTX



EULAR 2013 - D'après B. Terrier et al., abstr. OP0213,

B cell functions

Dominant APC during virus-nanoparticles immunization
Hong, 2018



Maheswari
Selvaraj, 2016

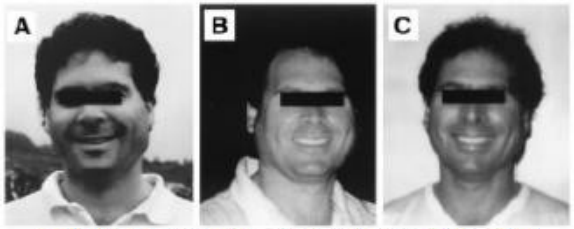
Agenda

- Pourquoi cibler les LB ?

- Comment cibler les LB ?
  - En les détruisant ? *Déplétion, faut-il aller plus profond ?*
  - En les modulant ? *Cibler la coactivation*
  - En éliminant les anticorps ? *Et notamment les autoanticorps*
  - En détruisant seulement les méchants ? *Le phantasme des thérapies ciblant les clones auto-réactifs*
  - En les rééduquant ? *Le phantasme de la vaccination par l'autoantigène*

- Où cibler les LB en France ?
  - La création du C3I

Sjögren's and rituximab



Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 49, No. 3, June 15, 2003, pp 394–398

Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 57, No. 2, March 15, 2007, pp 310–317
DOI 10.1002/art.22536

ORIGINAL ARTICLE

Improvement of Sjögren's Syndrome After Two Infusions of Rituximab (Anti-CD20)

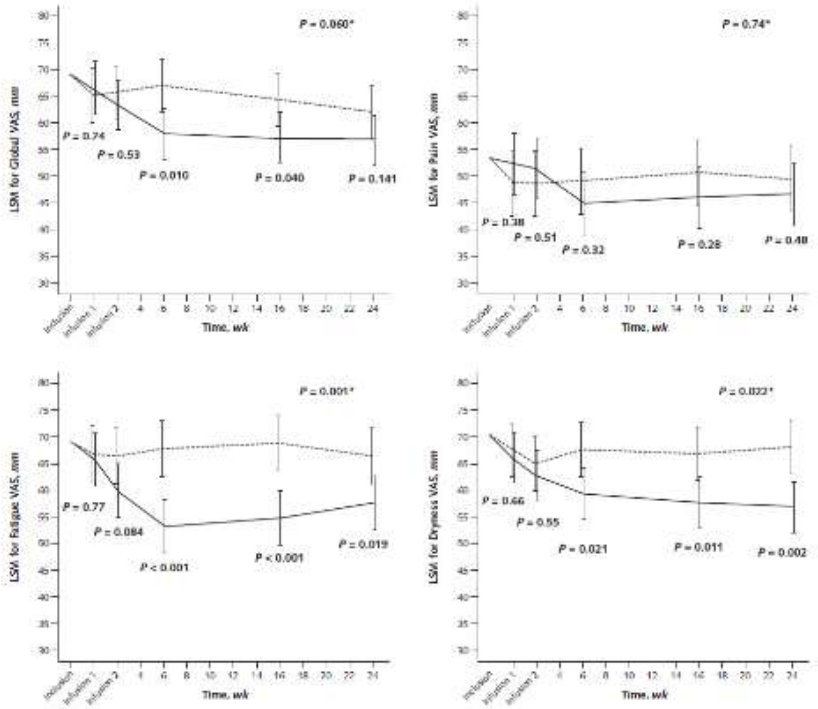
VALÉRIE DEVAUCHELLE-PENSEC,[1] YVON PENNEC,[†] JOHANNE MORVAN,[2] JACQUES-OLIVIER PERS,[3] CAPUCINE DARIDON,[3] SANDRINE JOUSSE-JOULIN,[2] ANNE ROUDAUT,[2] CHRISTOPHE JAMIN,[3] YVES RENAUDINEAU,[3] ISABELLE QUINTIN ROUÉ,[3] BÉATRICE COCHENER,[3] PIERRE YOUINOU,[3] AND ALAIN SARAUX[1]

Table 1. Clinical and laboratory test result changes from baseline to weeks 12, 24, and 36*

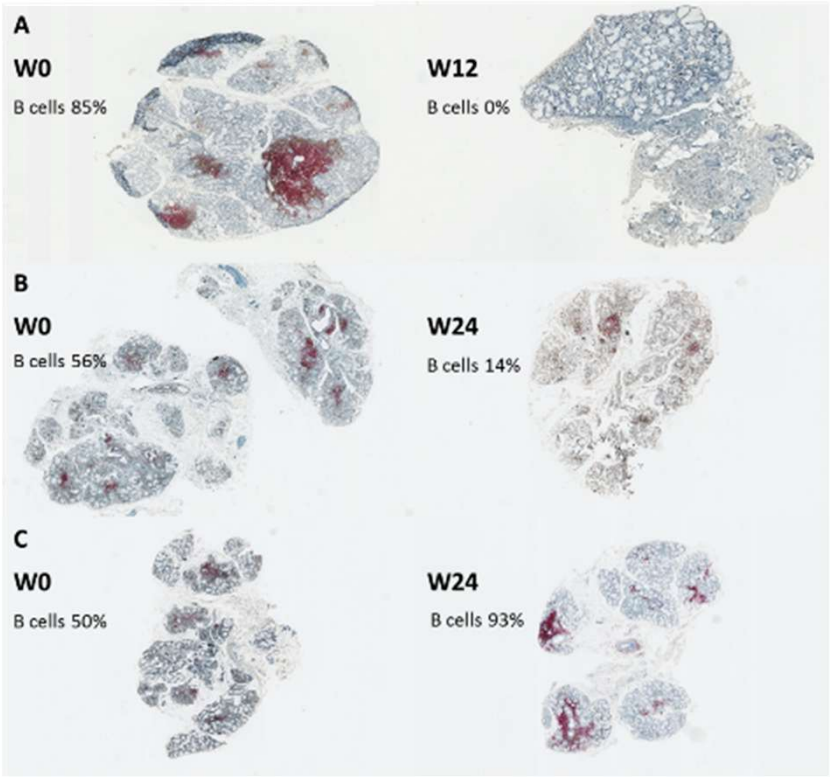
	Week 0	Week 12	*P* Weeks 0–12	Week 24	*P* Weeks 0–24	Week 36	*P* Weeks 0–36
Global disease VAS, mm	71.9 ± 13.4	64.3 ± 23.2	0.53	56.4 ± 26.6	0.033†	55 ± 30	0.03†
Pain VAS, mm	60.4 ± 19.2	48.8 ± 28.3	0.19	40.6 ± 25.5	0.02†	33 ± 28	0.006†
Fatigue VAS, mm	77.3 ± 14.5	56.9 ± 28.4	0.001†	54.6 ± 30.2	0.005†	58 ± 31	0.006†
Dryness VAS, mm	8.4 ± 11.9	57.6 ± 29.3	0.036†	52.4 ± 32.5	0.005†	53 ± 30	0.006†
Tender point count	4.5 ± 6	2.0 ± 5.2	0.035†	1.0 ± 1.5	0.049†	2.0 ± 4.7	0.027†
Tender joint count	6.0 ± 10.9	4.8 ± 11.7	0.175	1.8 ± 4.8	0.16	2.7 ± 9.8	0.017†
Swollen joint count	1.0 ± 0.9	0.3 ± 0.6	0.94	0 ± 0	0.16	0 ± 0	0.15
Salivary flow rate, ml/minute	0.1 ± 0.1	0.1 ± 0.1	0.35	0.18 ± 0.26	0.35	0.12 ± 0.1	0.86
Schirmer test, mm	8.4 ± 8.3	8.1 ± 8.86	0.95	7.1 ± 7.5	0.63	9.0 ± 7.8	0.79

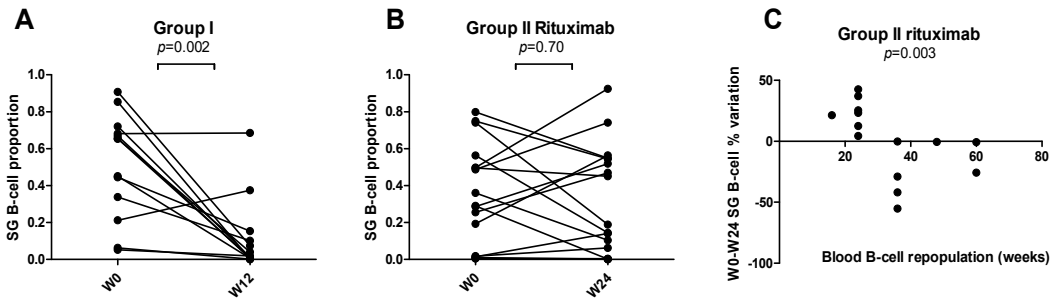
TEARS

	Week 24			
	Rituximab	Placebo	Difference (95% CI)	*P* Value
Patients with ≥30-mm improvement in VAS score, %†				
≥2 of 4 VASs‡	23.0	22.0	1.0 (−16.7 to 18.7)	0.91
Global	16.9	24.0	−7.1 (−19.1 to 4.9)	0.25
Pain	12.6	22.0	−9.4 (−26.7 to 8.0)	0.29
Fatigue	20.1	10.8	9.3 (−2.0 to 20.5)	0.105
Dryness	25.6	13.2	12.4 (−3.0 to 27.8)	0.114



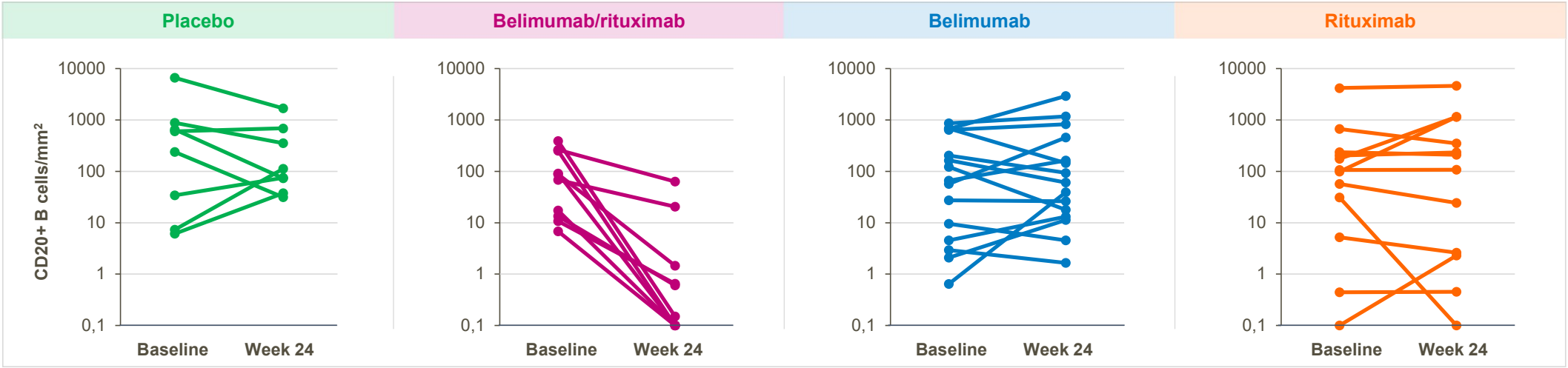
Salivary gland B-cell dynamics mirror blood B-cell depletion and repopulation





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)

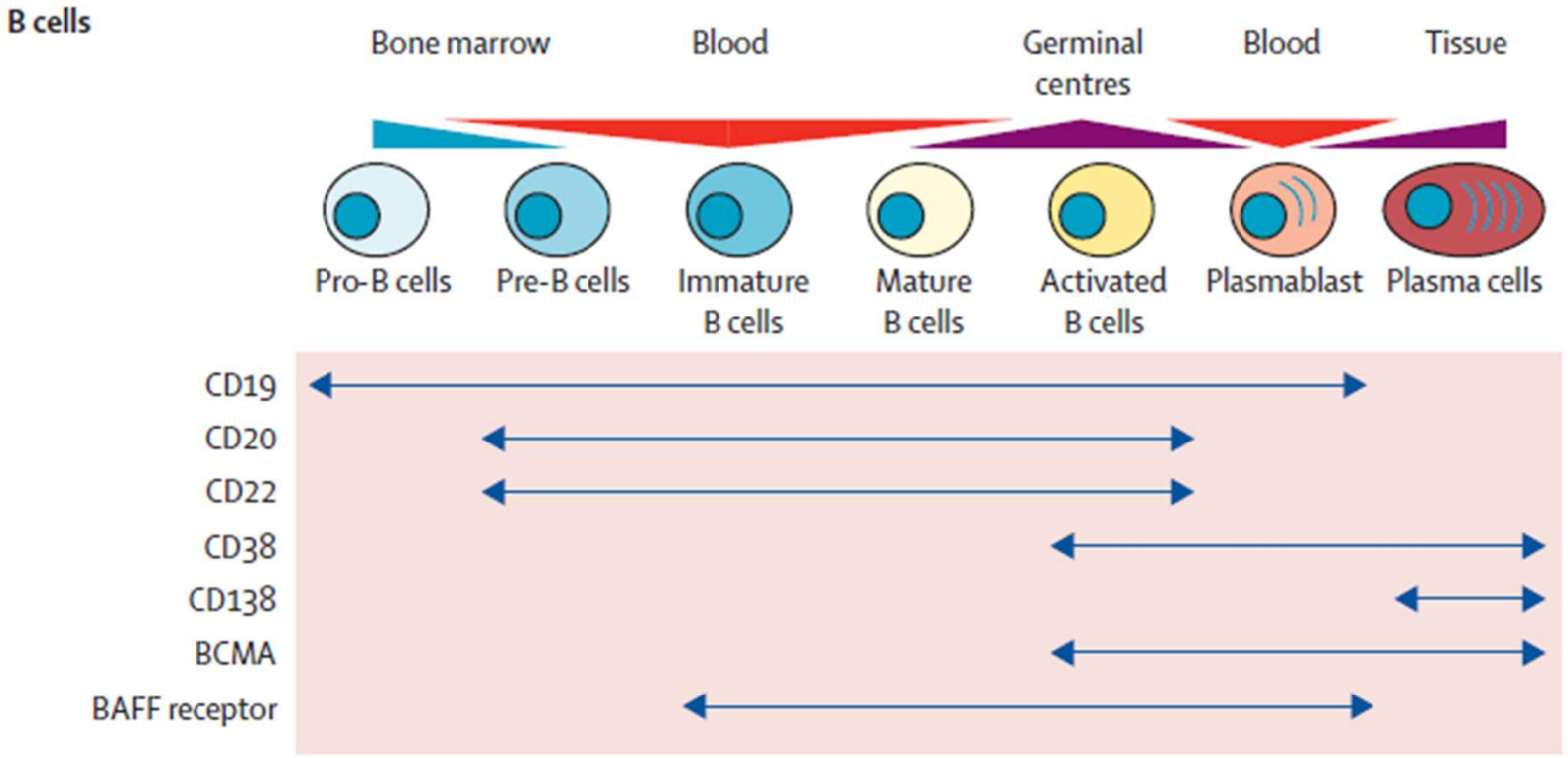


Median (IQR) absolute number of CD20+ B cells/mm²	Placebo		Belimumab/rituximab		Belimumab		Rituximab	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
	418 (21–763) n=8	93 (55–518) n=8	88 (13–252) n=15	0 (0–1) n=10	66 (5–636) n=19	61 (13–455) n=15	106 (31–235) n=13	158 (2–745) n=12

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

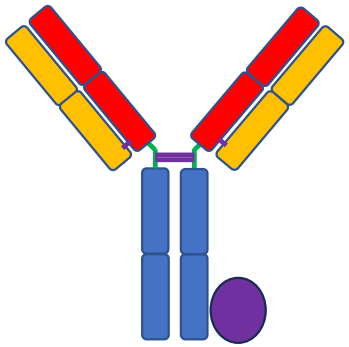
D’autres cibles sur les LB ?



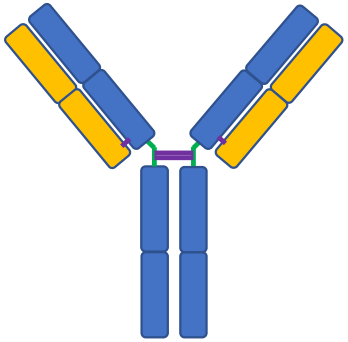
Comment améliorer la déplétion B ?

Améliorer les monoclonaux

Rituximab



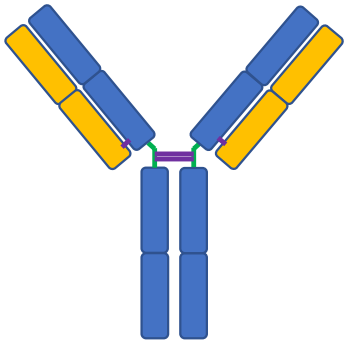
Obinutuzumab



ADCC ↗

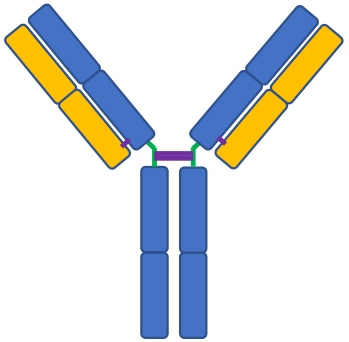
Diversifier les cibles

Ianalumab



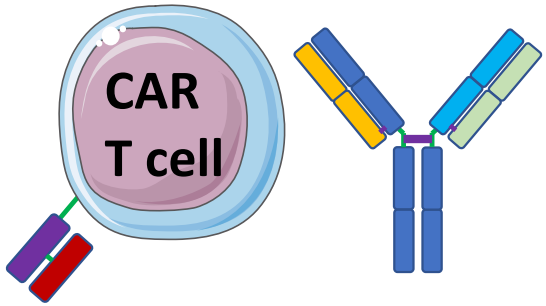
ADCC ↗

Inebilizumab



ADCC ↗

Immunothérapies intensives



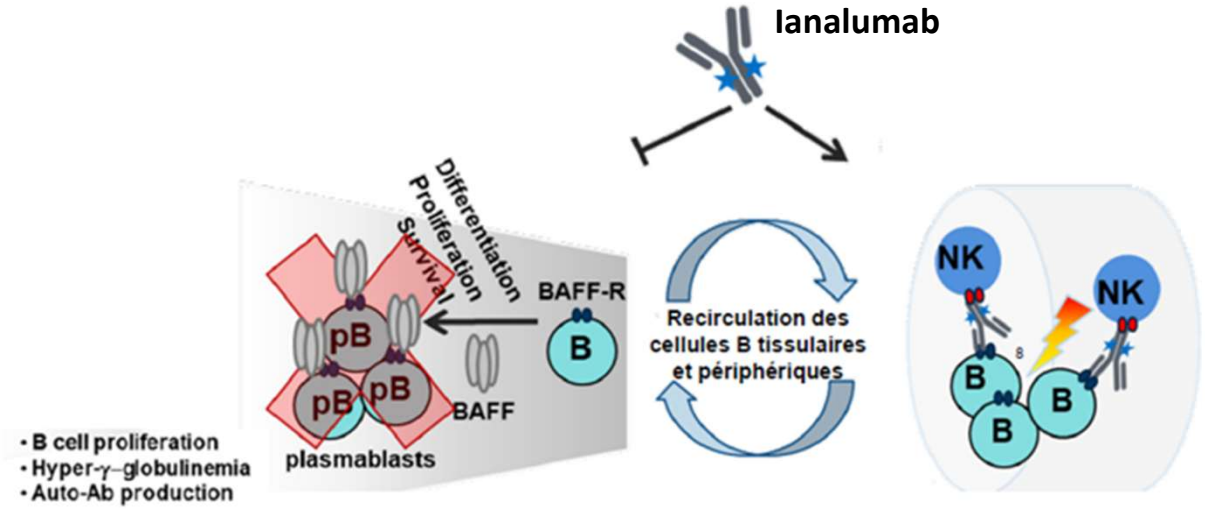
Cytotoxicité ↗ ↗

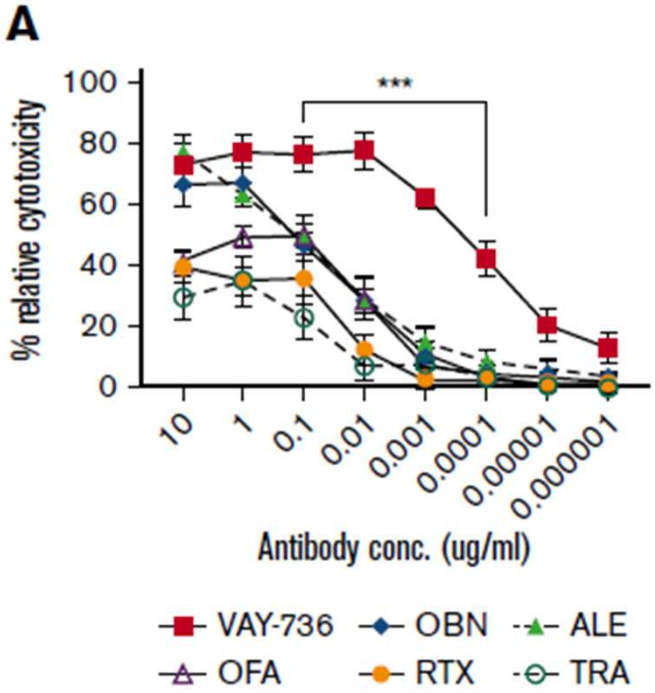
Anti-CD20

Anti-BAFFR

Anti-CD19

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





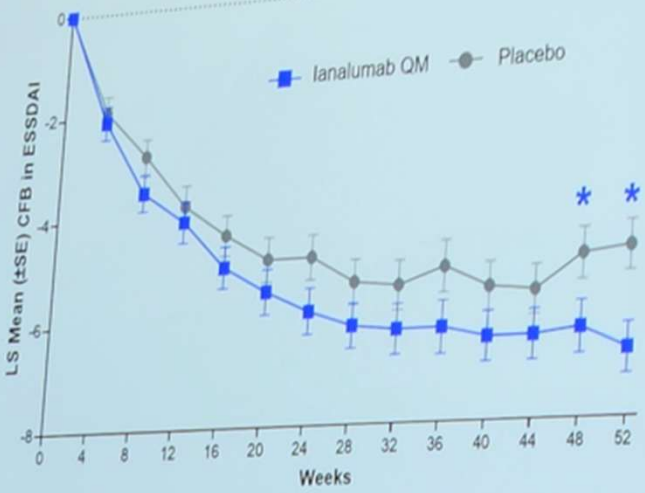
McWilliams EM et al. Blood Adv. 2019 Feb 12;3(3):447-460.


Oral presentation: LB24
Date and time: October 29 2025, 9:15 AM – 9:30 AM
Session: (LB19-LB24) Late-Breaking Abstracts
Thomas Grader-Beck
tgrader1@bwh.edu
Ianalumab demonstrates significant reduction in disease activity in patients with Sjögren's Disease: Efficacy and safety results from two global Phase 3, randomized, placebo-controlled double-blind studies (NEPTUNUS-1 and NEPTUNUS-2)
Thomas Grader-Beck*, Xavier Mariette*, Stephanie Finzel, Elena Schiopu, Athena Papas, Valerie Devauchelle-Pensec, Thomas Dörner, Monika Sopaia, Xiaofeng Zeng, Ghalib Noaiseh, Tsutomu Takeuchi, Uma Kumar, Josef Hermann, Hiroki Ozawa, Robert Fox, Susan Zong, Deepak Narayanswamy, Xiaomei Li, Wan-Lin Luo, Janice Wozniak, Laurie Deboraett, Xuan Zhu, Linchen He, Franziska Matzkies, Angelika Jahreis, Brian Porter, Sara McCoy, Simon J. Bowman, Wolfgang Huebel
Scan to download a copy of this presentation
*Contributed equally
ACR Convergence

The primary objective was met in both NEPTUNUS-1 and NEPTUNUS-2

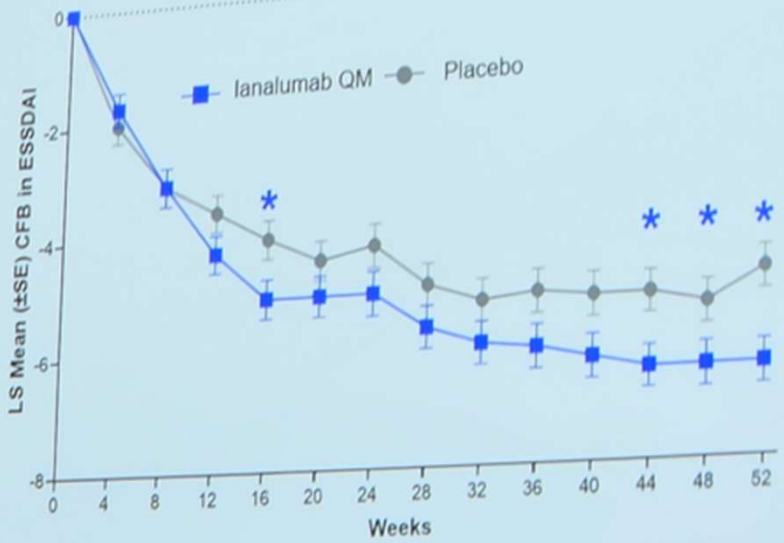
Ianalumab 300 mg monthly demonstrated statistically significant improvement in ESSDAI change from baseline at Week 48 compared with placebo in both studies

NEPTUNUS-1



Treatment	CFB in ESSDAI at Week 48** LS mean (SE)	Δ LS mean (SE)	95% CI	p-value
Ianalumab QM (N=137)	−6.4 (0.47)	−1.3 (0.66)	(−2.6, 0.0)	0.0496
Placebo (N=138)	−5.1 (0.46)			

NEPTUNUS-2



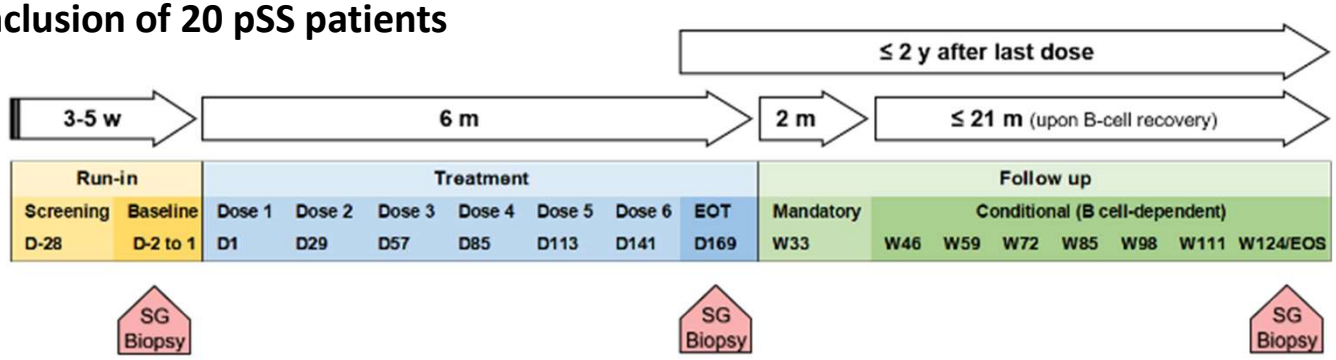
Treatment	CFB in ESSDAI at Week 48** LS mean (SE)	Δ LS mean (SE)	95% CI	p-value
Ianalumab QM (N=168)	−6.5 (0.36)	−1.0 (0.51)	(−2.0, 0.0)	0.041
Placebo (N=169)	−5.5 (0.35)			

*p<0.05. **ANCOVA model with study treatment, actual ESSDAI score stratum, and region as factors and baseline score as a covariate
ANCOVA, analysis of covariance; BL, baseline; CFB, change from baseline; CI, confidence interval; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; LS, least squares; N, number of patients in each treatment group of the specified analysis set; n, number of patients with evaluable data; QM, monthly; Q3M, every 3 months; SE, standard error.

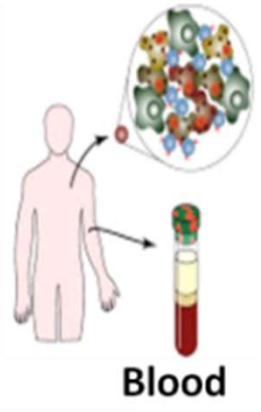
Therapeutic trials with associated translational projects

A mechanistic study to understand the mechanism of action of Ianalumab for pSS

Inclusion of 20 pSS patients



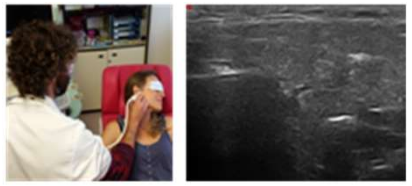
NOVARTIS



Immunophenotyping (IMC Hyperion)
Transcriptomics (scRNA Seq)

Immunophenotyping (CyTOF)
Transcriptomics (scRNA Seq)
Cytokine profiling
Serum/saliva biomarker discovery
PK/PD

Salivary gland ultrasonography



P2296

Divi Cornec | divi.cornec@chu-brest.fr

Evaluation of the dual mode of action of ianalumab (VAY736) in the circulation and salivary gland tissue of patients with Sjögren Disease: results from a phase 2 mechanistic study

Divi Cornec,[1] Rainer Hillenbrand,[2] Patrice Hemon,[3] Marion Le Rochais,[1] Diego Saldana Miranda,[2] Aida Santos Da Costa,[2] Marie Frutoso,[3] Cristian Iperi,[3] Ulrike Sommer,[2] Tala Shekarian,[2] Arnaud Uguen,[1] Christophe Jamin,[1] Patricia Baley,[4] Caroline Denis,[4] Dewi Guellec,[1] Alice Tison,[1] Daniel Strasser,[2] Sandrine Jousse-Joulin,[1] Shuqi Chen,[5] Noemi Giglioli,[2] Carole Sips,[2] Isabelle Isnardi,[2] Sumanta Barman,[2] Enrico Ferrero,[2] Nils Eling,[2] Grazyna Wieczorek,[2] Alain Saraux,[1] Richard Siegel,[2] Wolfgang Hueber,[2] Sophie Hillion,[1] Valérie Devauchelle-Pensec,[1] Claire Bonal[2]

[1]LBAI, UMR1227, University of Brest, CHU Brest, Brest, France; [2]Novartis Pharma AG, Basel, Switzerland; [3]LBAI, UMR1227, University of Brest, Brest, France; [4]CHU Brest, Brest, France; [5]China Novartis Institutes for BioMedical Research, Shanghai, China

CONCLUSIONS

- Treatment with ianalumab 300 mg monthly reduced B cell counts in circulation by 99% and B cell density in labial SG tissue by 84%, in line with the observed improvements in clinical and serological parameters at Week 25 compared to placebo
- Additionally, ianalumab 300 mg monthly modified the phenotype of the remaining B cells in circulation and in SG tissue, reducing the proportion of CXCR5+ B cells known to infiltrate lymphoid structure in labial salivary glands of SjD patients. These findings shed new light on the relevance of BAFF-R blockade in the dual mechanism of action of ianalumab, particularly on BAFF:BAFF-R-dependent CXCR5 role in the SjD[5]

Scan to obtain:
- Poster

To download a copy of this poster, visit the web at:
https://medicalcongressposters.com/Default.aspx?doc=a57b

This study was sponsored by Novartis Pharma AG, Basel, Switzerland.

Poster presented at the American College of Rheumatology Convergence, October 24–29, 2025, McCormick Place Convention Center in Chicago, Illinois, United States.

INTRODUCTION

- Sjögren disease (SjD) is a systemic, heterogeneous, autoimmune disease with substantial disease burden, high unmet need, and no approved systemic treatments[1]
- B cell hyperactivity and dysregulated B cell-activating factor/receptor (BAFF/BAFF-R) signalling are a hallmark of SjD pathogenesis[2]
- SjD is characterized by the infiltration of immune cells in exocrine glands, notably in the salivary glands (SG), as focal aggregates of B and T cells around ducts[3]
- Ianalumab is a fully human IgG1 monoclonal antibody with a novel dual mechanism of action that depletes B cells through enhanced antibody-dependent cellular cytotoxicity (ADCC) and also inhibits their activation and survival via BAFF-R blockade[4]
- The purpose of this mechanistic biopsy-based study is to better understand the dual mechanism of action of ianalumab in the blood and the SG tissue of patients with SjD

METHODS

Study Design and Interventions

- This is a single-arm open-label phase 2 mechanistic study (NCT05124925) with a 5-week screening period, a 6-month treatment period and a follow-up period for up to 2 years after the last dose

Patients

- Patients with confirmed SjD according to the 2016 ACR/EULAR classification criteria, seropositive for anti-Ro/ Sjögren's syndrome antigen A (SSA) antibodies, EULAR Sjögren's Syndrome Patient-Reported Index score (ESSPRI) ≥5, labial SG biopsy focus score of ≥0.3/4 mm², and B/B+T cell ratio of ≥0.2 at screening were included

Treatment

- During the treatment period, patients received ianalumab 300 mg subcutaneously every month for 6 months

Outcomes

- The primary outcome was change in the B/B+T cell ratio seen on labial SG biopsy from Baseline to Week 25. Other outcomes included mass cytometry and single-cell RNA sequencing of circulating immune cells and labial SG histology and imaging mass cytometry, as well as clinical evaluations, safety, and tolerability
- Patients' blood samples and labial SG biopsies were collected pre-treatment and at Week 25. Labial SG biopsies were fixed and paraffin embedded. Sections were stained with H&E, CD3 and CD20 on the Ventana Ultra (Roche, Mannheim, Germany). Focus score, B/B+T cell ratio, and B cell densities were analyzed via manual counting
- For CyTOF analysis, fresh blood samples were stained with a panel of 40 metal-labelled markers including extracellular and intracellular staining, designed for immunophenotyping (panel 1) and mapping of T (panel 2) and B cell subsets (panel 3). Data were acquired in batches including samples taken at Baseline and Week 25 on CyTOF II (Fluidigm, USA) following the Helios instructions and software normalized to internal bead standards. B-cell related data were subjected to supervised analysis following a preset gating strategy for the various cell types
- For single-cell RNAseq analysis, peripheral blood mononuclear cells were isolated by Ficoll gradient method from whole blood. Single cell suspensions targeting approximately 20,000 cells per sample were loaded onto a 10x Genomics Chromium. After single cell capture, libraries were generated using the GEM-X, Single Cell 5' v3 gene expression kits. Libraries were pooled and sequenced on a NovaSeq 6000 (Illumina) following manufacturer instructions. Processing of single-cell RNASeq data was performed using scanpy. Steps included contamination estimation (decontX), integration (harmony), clustering (Leiden), pre-annotation (celltypist), majority voting, and final manual cluster merging and curation. Pseudobulk differential gene expression was performed using limma trend and comparing Week 25 (end-of-treatment) with Baseline samples
- Hyperion imaging mass cytometry was performed using the standard protocol. Following tissue deparaffinization and antigen retrieval, samples were stained with a cocktail of 41 metal-conjugated antibodies and incubated over night, then counterstained with Cell-ID Intercalator-Ir (125 µM). Regions of interest (1.5 mm²) were selected based on CD20 and CD3 IHC from an adjacent section and acquired by laser ablation at 200 Hz using the standard Hyperion imaging mass cytometry protocol

RESULTS

Patient disposition

- This primary interim analysis was performed after all patients had received all 6 doses and underwent post-treatment biopsy at 6 months or discontinued treatment earlier
- Of the 34 patients who consented, 13 failed the screening. Among the 11 participants who did not meet the criteria for labial SG focus score and/or B/B+T cell ratio, 4 were successfully rescreened. Among the 21 treated with ianalumab, 20 received all 6 monthly doses and underwent paired screening and Week 25 biopsy (n=17)
- Of these 20 participants, 17 completed the treatment period without important protocol deviations (prohibited medication, visit outside the protocol window)

Baseline characteristics

- The baseline disease characteristics were as follows: Mean (SD) EULAR Sjögren's syndrome disease activity index (ESSDAI) 8.05 (4.43); ESSPRI 7.02 (1.35); Focus score 2.724 mm² (4.06); B/B+T cell ratio 0.52 (0.11)

Safety

- In the safety analysis set (N=21), ianalumab was well tolerated with no drug-related serious adverse events (AEs) and one AE leading to discontinuation

Pharmacodynamics

- Clinical outcomes improved numerically in the 17 patients (Table 1)

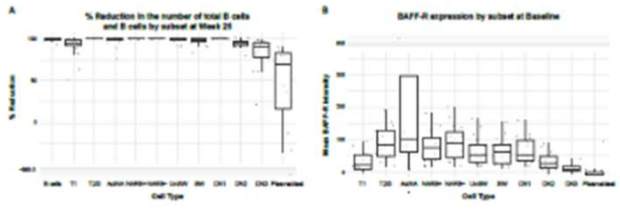
Table 1 Clinical outcomes

Characteristic	Baseline Mean (SD)	Week 25 Mean (SD)	Change from Baseline (mean with 95% CI)
ESSDAI	8.8 (4.6)	7.3 (4.7)	−1.5 (−3.16, 0.1)
ESSPRI	7.0 (1.4)	4.7 (2.4)	−2.3 (−3.41, −1.1)
PhGA	39.0 (11.3)	24.4 (8.8)	−14.6 (−21.41, −7.77)
PaGA	63.6 (16.1)	44.5 (26.8)	−18.9 (−28.13, −9.76)
IDEEL	63.1 (19.6)	50.0 (26.1)	−13.1 (−21.92, −4.26)
Stimulated salivary flow rate (mL/min)	0.6 (0.7)	0.7 (0.8)	0.2 (0.01, 0.33)
Unstimulated salivary flow rate (mL/min)	0.1 (0.1)	0.1 (0.2)	0.0 (−0.03, 0.06)
Average Schirmer's test	3.7 (4.6)	6.2 (8.5)	2.4 (0.09, 4.8)

ESSDAI, EULAR Sjögren's syndrome (SS) disease activity index; ESSPRI, EULAR Sjögren's Syndrome Patient-Reported Index; IDEEL, Impact of Dry Eye Disease on Everyday Life; PaGA, Patient's global assessment; PhGA, Physician's Global Assessment of Disease Activity

- CyTOF analysis (n=20) demonstrated that monthly treatment with ianalumab 300 mg led to an almost complete depletion of circulating CD19+ B cells decreasing by 99% compared to baseline, as also shown by flow cytometry and scRNAseq (not shown)
- B cells were almost completely depleted in most subsets, namely transitional, naive, unswitched and switched memory B cells and to a lower extent in double negative effector memory cells (89.5%) and plasmablasts (89.5%)
- The median reduction of B cells by subset was significantly correlated with their median BAFF-R expression at Baseline, both at the protein level (mass cytometry) and mRNA level (single cell RNAseq) (p=0.008 for both) (Figure 1)

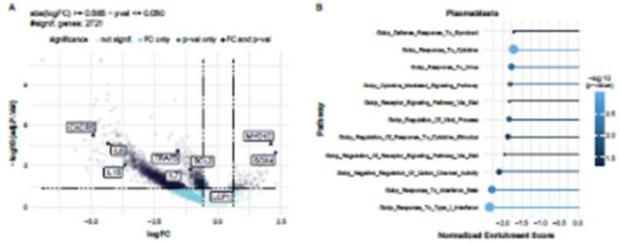
Figure 1. Reduction in the number of circulating B cells at Week 25 (A) in relation to BAFF-R expression at Baseline (B)



ActNA, activated naive cells; BAFF-R, B cell-activating factor receptor; BL, Baseline; CD, cluster of differentiation; DN1-3, double negative effector memory cells; NAIVE, naive cells (CD45RB); SM, switched memory cells; T1-3, transitional cells; UnSM, unswitched memory cells

- Differential gene expression analysis (n=20) revealed downregulation of B cell signalling, proliferation (BCL2), chemotaxis (CXCR5), cytokines (IL6, IL15), NF-kB related genes (TRAF5), and upregulation of genes having roles in B cell development (LCP1, SOX4) and B cell cytoskeleton arrangement (MYO1C) in the remaining naive B cells present at Week 25 (Figure 2)
- In addition, Gene Set Enrichment Analyses (GSEA) found IFN gene sets to be downregulated in plasmablasts at Week 25

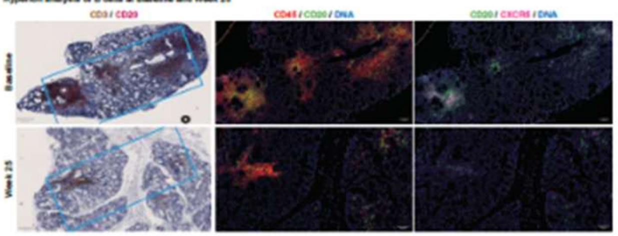
Figure 2. Week 25 vs Baseline pseudobulk differential expression analysis volcano plot for naive B cells (A) and GSEA in plasmablasts (B)



Histological changes

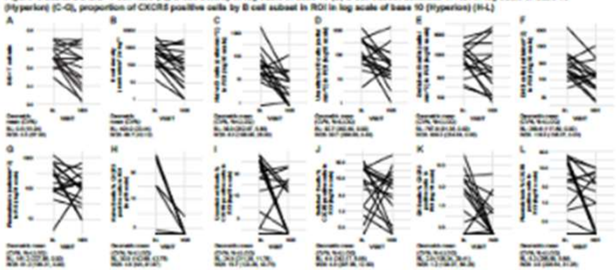
- In the labial salivary gland, the extent of inflammatory infiltrate composed of B and T cells diminished at Week 25 vs Baseline as seen on these representative CD3/CD20 IHC stained sections (Figure 3)

Figure 3. A representative example of labial salivary gland biopsy section stained for CD3/CD20, including ROI in blue, and section stained for Hyperion analysis of B cells at Baseline and Week 25



- While the focus score was only slightly reduced (not shown), based on regression analyses, the B/B+T cell ratio was statistically significantly reduced by 41% (80% CI: 22%, 55%) and the B cell density was reduced by 84% (80% CI: 68%, 91%) at Week 25 vs Baseline (n=17)
- In the region of interest (ROI) centered on a focus, the density of naive, unswitched and switched memory and double negative B cells assessed by Hyperion decreased at Week 25 vs Baseline, mirroring the reduction of B cells by subsets seen in blood (n=17) (Figure 4). In the naive, unswitched B cells, and plasmablast subsets, the proportion of CXCR5 positive B cells, known to traffic to lymphoid structures, decreased at Week 25 vs Baseline (n=17)

Figure 4. Labial SG B/B+T cell ratio (A), B cell density in log scale of base 10 (B) B cell subset densities in ROI in log scale of base 10 (Hyperion) (C-G), proportion of CXCR5 positive cells by B cell subset in ROI in log scale of base 10 (Hyperion) (H-L)



BL, Baseline; SG, salivary gland; W, week. Some patients had 0 naive B cells in the region of interest at W25 and one had 0 at BL. In these cases, a percentage of CXCR5+ cells was not possible to calculate.

References

1. Bowman SJ, et al. *Ann Rheum Dis*. 2025;84:1068–1080.
2. Nocturne G, et al. *Nat Rev Rheumatol*. 2018 Mar;14(3):133–145.
3. Verstappen, et al. *Nat Rev Rheumatol*. 2021;17:333–348.
4. McWilliams, et al. *Blood Adv*. 2019;3(3):447–460.
5. Koizumi K, et al. *Biochem Biophys Rep*. 2023;7(34):101451.

Acknowledgments

All authors participated in the development of the abstract. The authors thank Dominik Aschenbrenner, Sascha Kilmer, Jonas Zierer and David Schubert for their methodological guidance, and Sangeeta Dhanuka, BHMS, MBA (Novartis Healthcare Pvt Ltd, India) and Venkatesh Teedla, MS, CMPP (Novartis Healthcare Pvt Ltd, India) for editorial and medical writing support, which was funded by Novartis Pharma AG, Basel, Switzerland in accordance with Good Publication Practice (GPP 2022) guidelines (https://www.ismpp.org/gpp-2022).

Disclosures

D Cornec has no disclosures. P Hemon has no disclosures. M Le Rochais has no disclosures. M Frutoso has no disclosures. C Iperi has no disclosures. A Uguen has no disclosures. C Jamin has no disclosures. P Baley has no disclosures. C Denis has no disclosures. D Guellec has no disclosures. A Tison has received support from Celltrion Healthcare France for attending a Congress and is a Consultant for Galapagos. S Jousse-Joulin has no disclosures. A Saraux has received speaker's fee and honoraria from Novartis for speakers bureau, symposia, and as an expert witness. S Hillion has no disclosures. V Devauchelle-Pensec has received grant/research support, speaker's fee and honoraria for speakers bureau, symposia, and as an expert witness from AbbVie and Eli Lilly; speaker's fee and honoraria for speakers bureau, symposia, and as an expert witness from Galapagos, Alphasigma, and Chugai; and has been an advisor/review panel member for Novartis. R Hillenbrand, D Saldana Miranda, A Santos Da Costa, U Sommer, T Shekarian, D Strasser, S Chen, N Giglioli, C Sips, I Isnardi, S Barman, E Ferrero, N Eling, G Wieczorek, R Siegel, W Hueber, C Bonal are employees of Novartis and hold stock options or bond holdings in a for-profit corporation or self-directed pension plan.

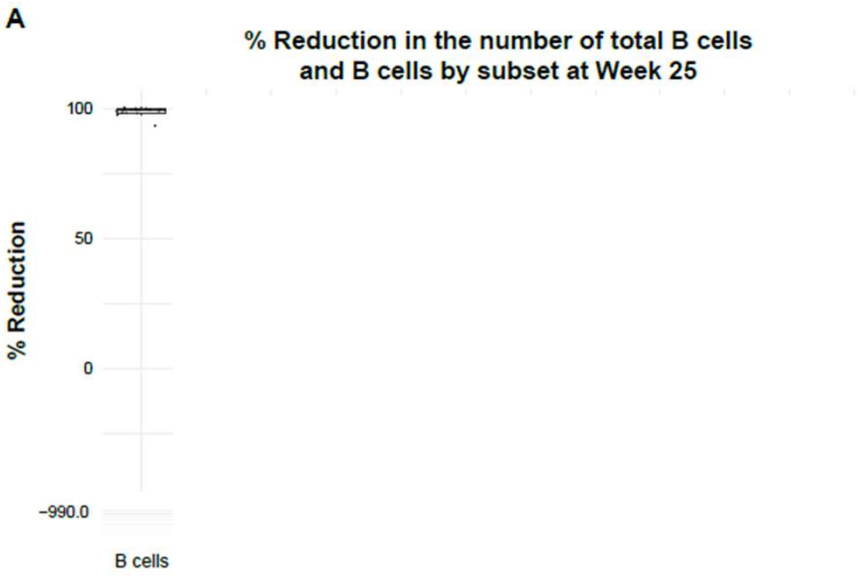
Table 1 Clinical outcomes

Characteristic	Baseline Mean (SD)	Week 25 Mean (SD)	Change from Baseline (mean with 95% CI)
ESSDAI	8.8 (4.6)	7.3 (4.7)	−1.5 (−3.16, 0.1)
ESSPRI	7.0 (1.4)	4.7 (2.4)	−2.3 (−3.41, −1.1)
PhGA	39.0 (11.3)	24.4 (8.8)	−14.6 (−21.41, −7.77)
PaGA	63.5 (16.1)	44.5 (25.8)	−18.9 (−28.13, −9.75)
IDEEL	63.1 (19.6)	50.0 (26.1)	−13.1 (−21.92, −4.26)
Stimulated salivary flow rate (mL/min)	0.6 (0.7)	0.7 (0.8)	0.2 (0.01, 0.33)
Unstimulated salivary flow rate (mL/min)	0.1 (0.1)	0.1 (0.2)	0.0 (−0.03, 0.06)
Average Schirmer’s test	3.7 (4.8)	6.2 (8.5)	2.4 (0.09, 4.8)

ESSDAI, EULAR Sjögren's syndrome (SS) disease activity index; ESSPRI, EULAR Sjögren's Syndrome Patient-Reported Index; IDEEL, Impact of Dry Eye Disease on Everyday Life; PaGA, Patient's global assessment; PhGA, Physician's Global Assessment of Disease Activity.

Figure 1. Reduction in the number of circulating B cells at Week 25 (A) in relation to BAFF-R expression at Baseline (B)

A



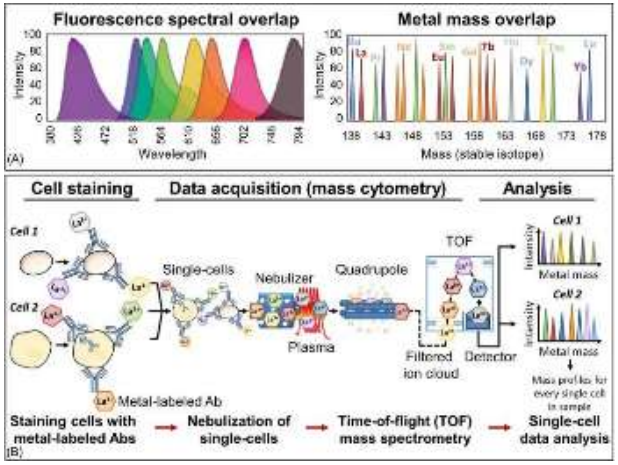
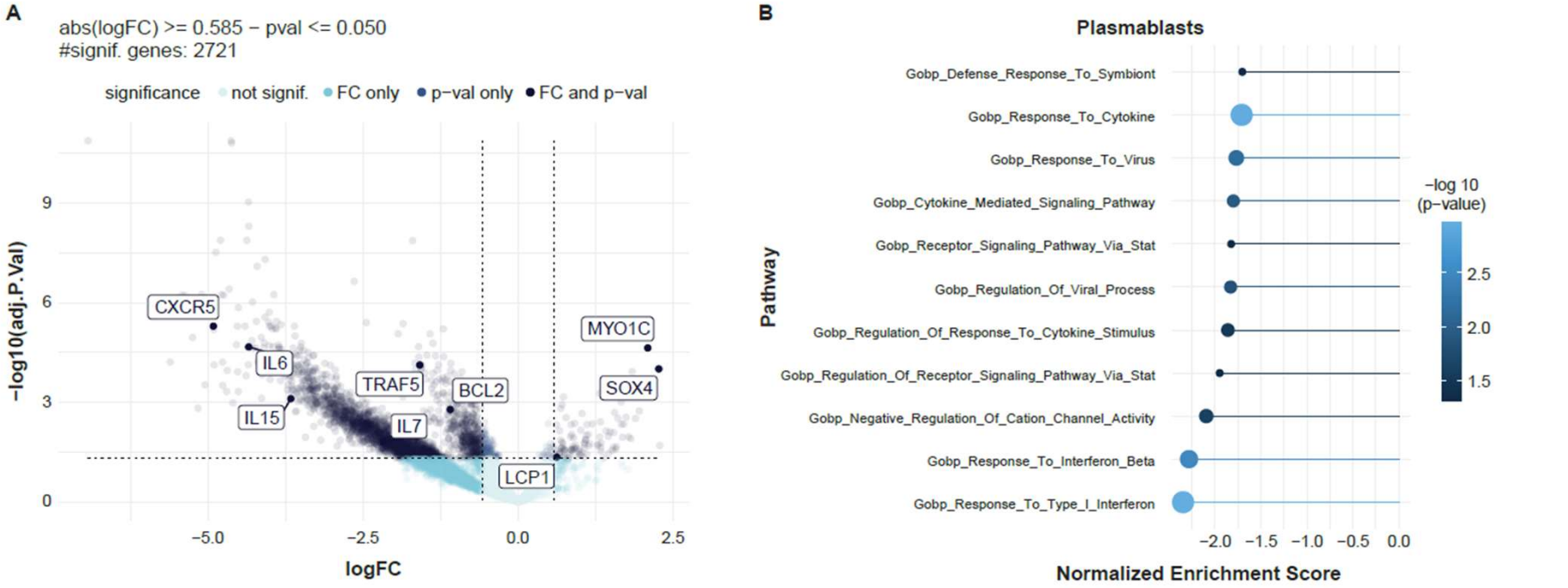
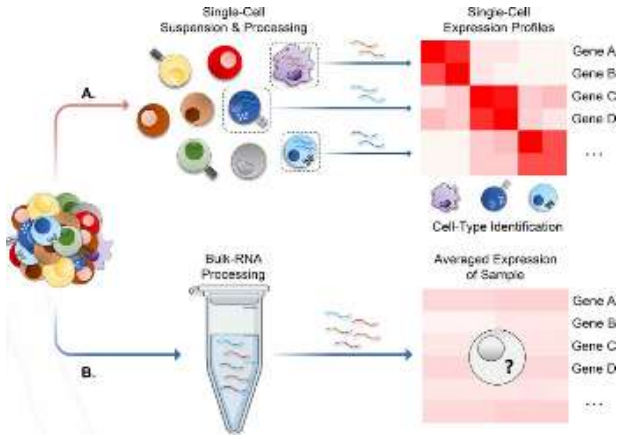


Figure 2. Week 25 vs Baseline pseudobulk differential expression analysis volcano plot for naïve B cells (A) and GSEA in plasmablasts (B)



Single-cell RNA seq



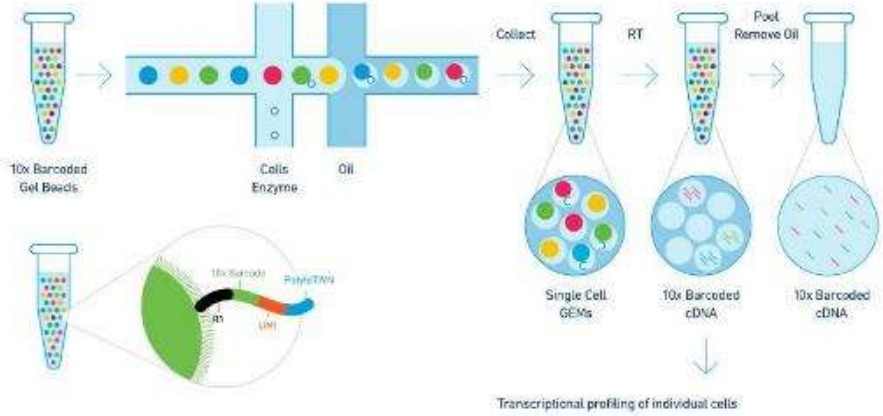
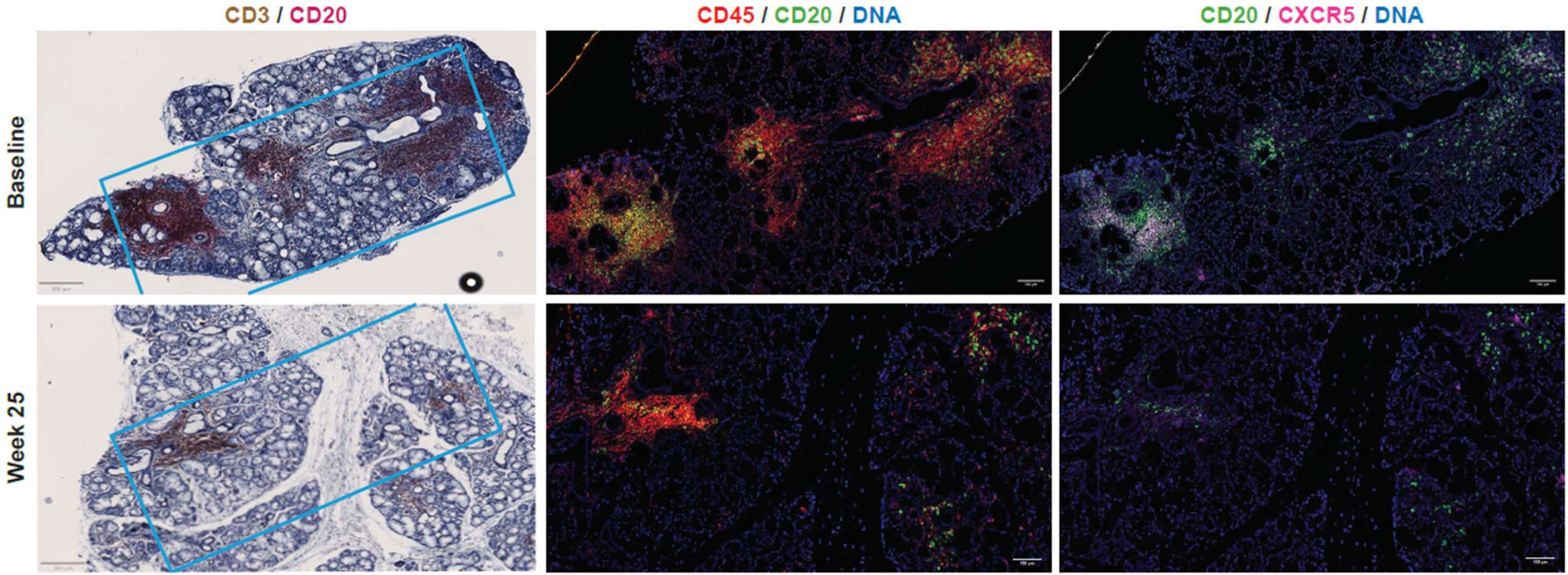


Figure 3. A representative example of labial salivary gland biopsy section stained for CD3/CD20, including ROI in blue, and section stained for Hyperion analysis of B cells at Baseline and Week 25



Comment dépléter plus/mieux les LB ?

- La révolution des CAR-T cells en hématologie

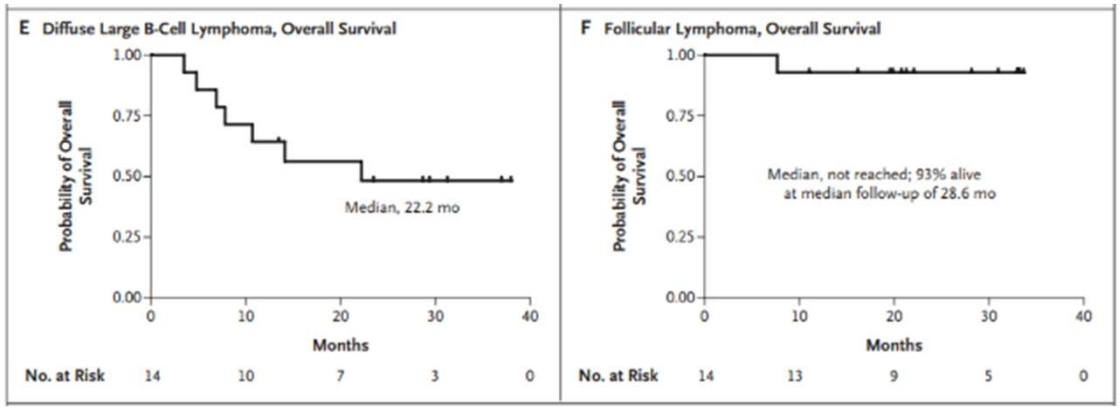
The NEW ENGLAND JOURNAL of MEDICINE

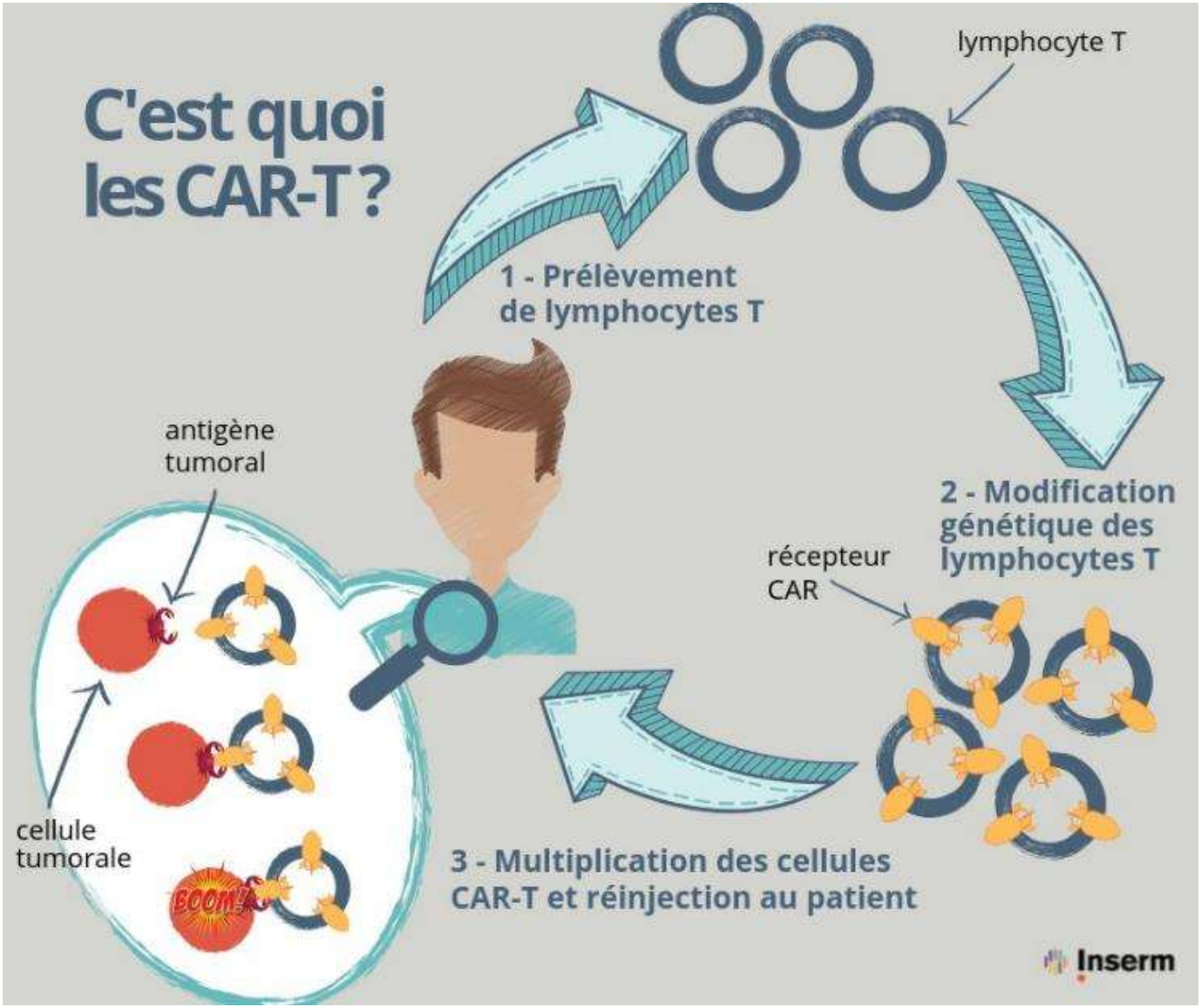
ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas

Stephen J. Schuster, M.D., Jakub Svoboda, M.D., Elise A. Chong, M.D., Sunita D. Nasta, M.D., Anthony R. Mato, M.D., Özlem Anak, M.D., Jennifer L. Brogdon, Ph.D., Iulian Pruteanu-Malinici, Ph.D., Vijay Bhoj, M.D., Ph.D., Daniel Landsburg, M.D., Mariusz Wasik, M.D., Bruce L. Levine, Ph.D., Simon F. Lacey, Ph.D., Jan J. Melenhorst, Ph.D., David L. Porter, M.D., and Carl H. June, M.D.

N ENGL J MED 377;26 NEJM.ORG DECEMBER 28, 2017



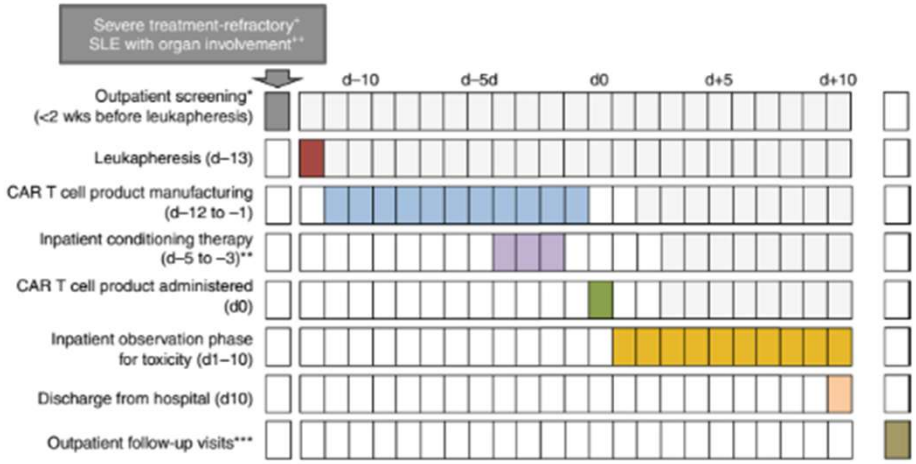

C'est quoi les CAR-T ?
lymphocyte T
1 - Prélèvement de lymphocytes T
2 - Modification génétique des lymphocytes T
récepteur CAR
antigène tumoral
cellule tumorale
BOOM !
3 - Multiplication des cellules CAR-T et réinjection au patient
Inserm

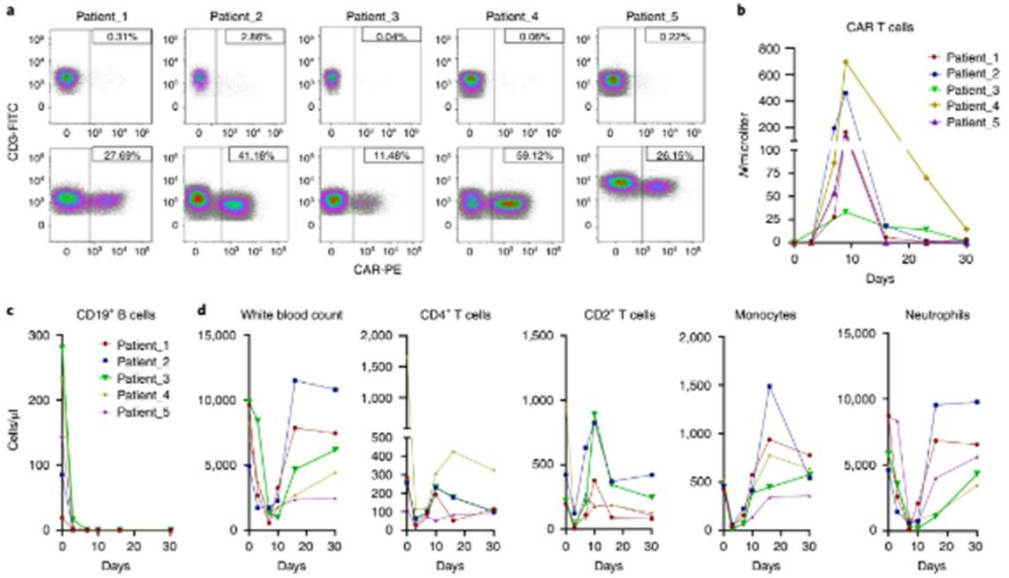
ARTICLES
https://doi.org/10.1038/s41591-022-02017-5
nature medicine

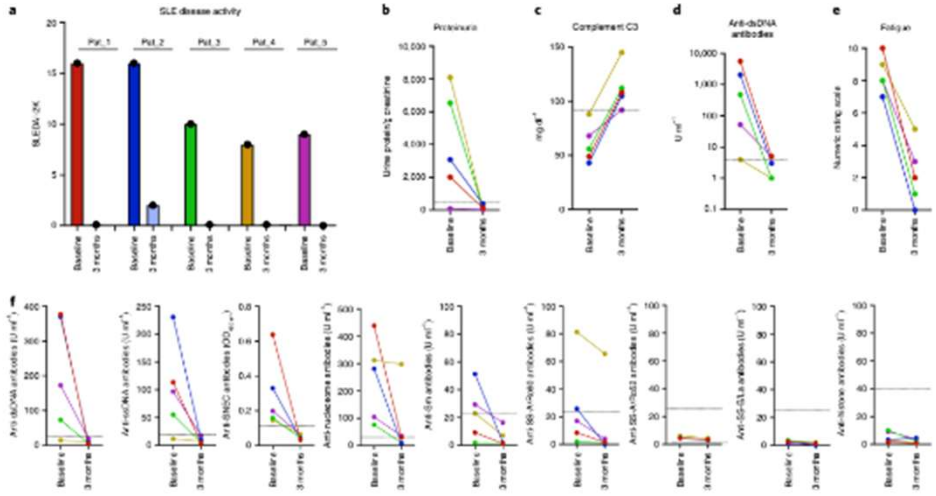
Check for updates

Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

Andreas Mackensen[1,2,8], Fabian Müller[1,2,8], Dimitrios Mougiakakos[1,2,3,8], Sebastian Böltz[2,4], Artur Wilhelm[2,4], Michael Aigner[1,2], Simon Völkl[1,2], David Simon[2,4], Arnd Kleyer[2,4], Luis Munoz[2,4], Sascha Kretschmann[1,2], Soraya Kharboutli[1,2], Regina Gary[1,2], Hannah Reimann[1,2], Wolf Rösler[1,2], Stefan Uderhardt[2,4], Holger Bang[5], Martin Herrmann[2,4], Arif Bülent Ekici[6], Christian Buettner[6], Katharina Marie Habenicht[7], Thomas H. Winkler[7], Gerhard Krönke[2,4,8] and Georg Schett[2,4,8] ✉







Ann Rheum Dis 84 (2025) 106–114

Contents lists available at ScienceDirect

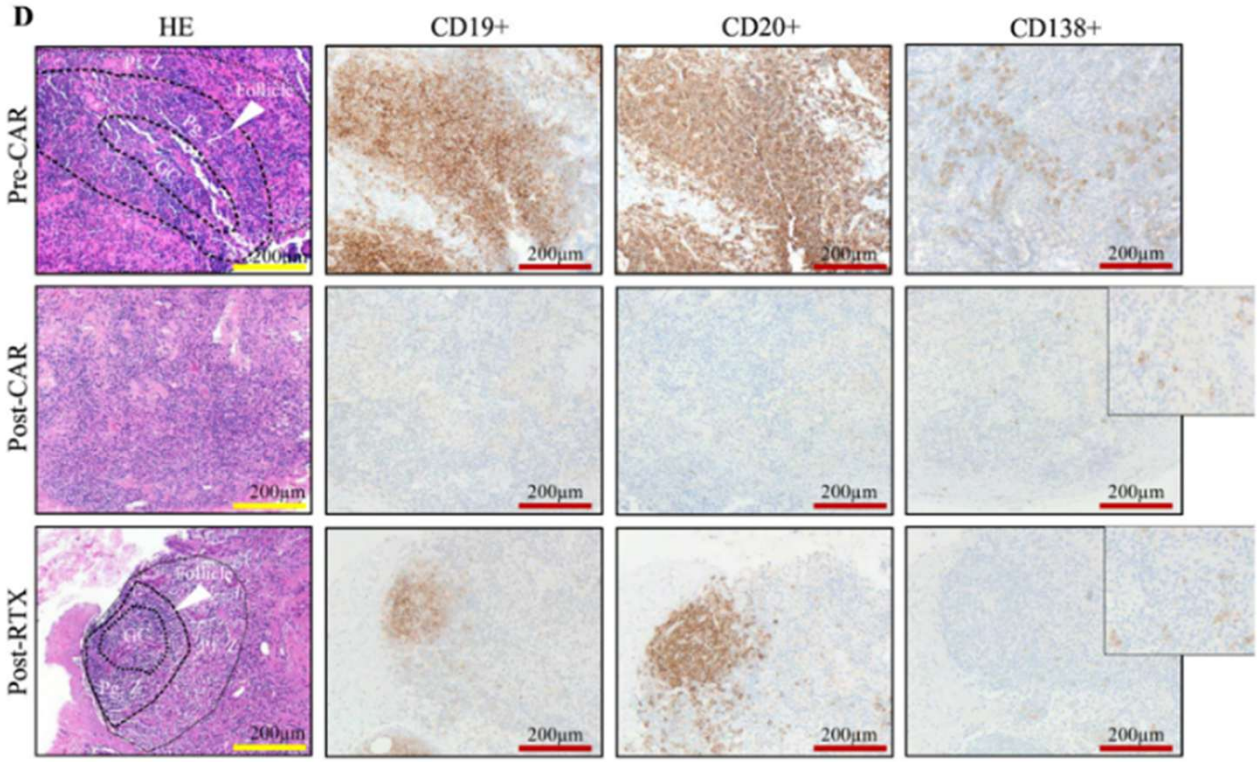
Annals of the Rheumatic Diseases

journal homepage: https://www.sciencedirect.com/journal/annals-of-the-rheumatic-diseases

Autoimmunity

CD19-CAR T-cell therapy induces deep tissue depletion of B cells

Carlo Tur[1,2,3], Markus Eckstein[4], Joachim Velden[5], Simon Rauber[1,2], Christina Bergmann[1,2], Janina Auth[1,2], Laura Bucci[1,2], Giulia Corte[1,2], Melanie Hagen[1,2], Andreas Wirsching[1,2], Ricardo Grieshaber-Bouyer[1,2], Petra Reis[1,2], Nicolai Kittan[1,2], Jochen Wacker[1,2], Aleix Rius Rigau[1,2], Andreas Ramming[1,2], Maria-Antonietta D'Agostino[3], Arndt Hartmann[4], Fabian Müller[6], Andreas Mackensen[6], Aline Bozec[1,2], Georg Schett[1,2,3], Maria Gabriella Raimondo[1,2,*]



CAR T-cell therapy in autoimmune diseases: where are we and where are we going?

*Marc Scherlinger, Gaetane Noctume, Marko Radic, David Launay, Christophe Richez, Philippe Bousso, Edouard Forcade, Alain Meyer, Christian Jorgensen, Camille Bigenwald, Divi Cornec, Jean Sibilia, Sylvain Choquet, Thierry Martin, Alexandre Belot, Maurine Jouret, Samuel Bitoun, Zahir Amoura, Olivier Hermine, Xavier Mariette, Emmanuel Donnadieu, Jérome Avouac, on behalf of the Club for Innovative Immunotherapies in Immune-mediated Inflammatory diseases (C3I)**

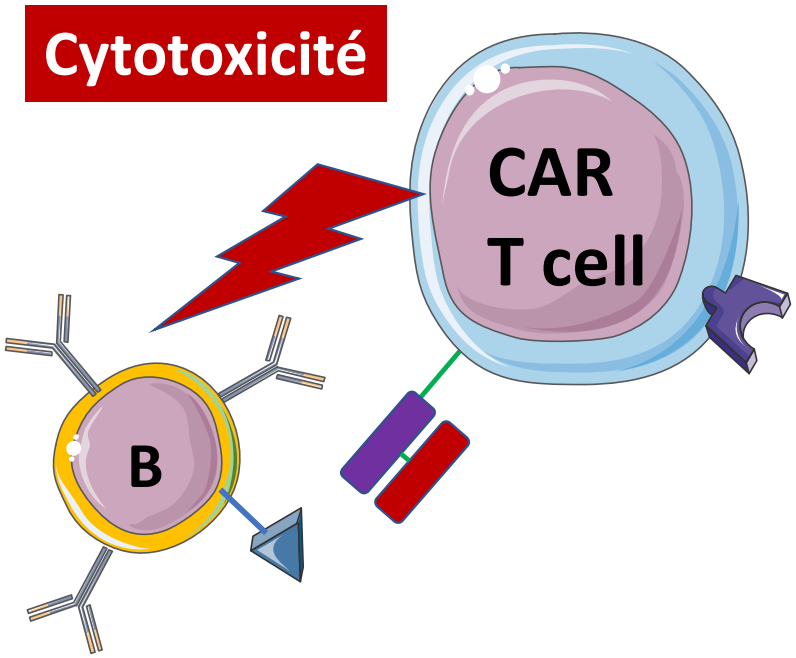
www.thelancet.com/rheumatology **Published online March 26, 2025** **https://doi.org/10.1016/S2665-9913(24)00377-1**

	SLE (P1–8)[14]	Idiopathic inflammatory myositis (P9–11)[14]	Systemic sclerosis (P12–17)[14,24]	Idiopathic inflammatory myositis (P18)[25]	Systemic sclerosis (P19)[26]	Idiopathic inflammatory myositis, juvenile dermatomyositis (P20)[27]
Conditioning or lymphodepleting chemotherapy	Fludarabine 25 mg per m² per day intravenously (3 days, days –5, –4, –3); cyclophosphamide 1000 mg per m² per day intravenously (1 day, day –3); patients #7 and #14 received 50% reduced dose	..	..	Fludarabine 25 mg per m² per day intravenously (3 days, days –5, –4, –3); cyclophosphamide 1000 mg per m² per day intravenously (1 day, day –3)	Fludarabine 30 mg per m² per day (3 days, days –4, –3, –2); cyclophosphamide 500mg per m² per day (3 days, days –4, –3, –2)	Fludarabine 90 mg per m² per day for 3 days (days –5, –4, –3); cyclophosphamide 1000mg per m² per day for 2 days (days –5, –4)
Longevity of clinical response	Up to 29 months; SLEDAI-2K=0; anti-dsDNA antibody negative; normalisation of C3; patient 4 had isolated rebound of proteinuria at 4 months	Up to 12 months; normalisation of creatine kinase; VAS-EM score=0; stabilisation of manual muscle testing-8 score; marked decrease of specific antibodies	Up to 20 months; disappearance of anti-RNA polymerase III antibody that was positive again after 400 days; decrease in anti-topo1 titres	Up to 150 days; improvement of patient performance and pulmonary function tests; marked reduction of anti-Jo1 antibodies at day 210	11 months; stabilisation of mRSS and pulmonary function tests; no detection of anti-Scl70 antibodies	8 months follow-up with continued improvement
Corticosteroid and immunosuppressor discontinuation	Discontinuation of corticosteroids and all immunosuppressive drugs as of the final follow-up	..	..	Discontinuation of corticosteroids; mycophenolate mofetil ongoing	Discontinuation of mycophenolate mofetil at month 9; nintedanib ongoing	Patient received methylprednisolone between leukapheresis and CAR T-cell infusion, then all treatment was stopped

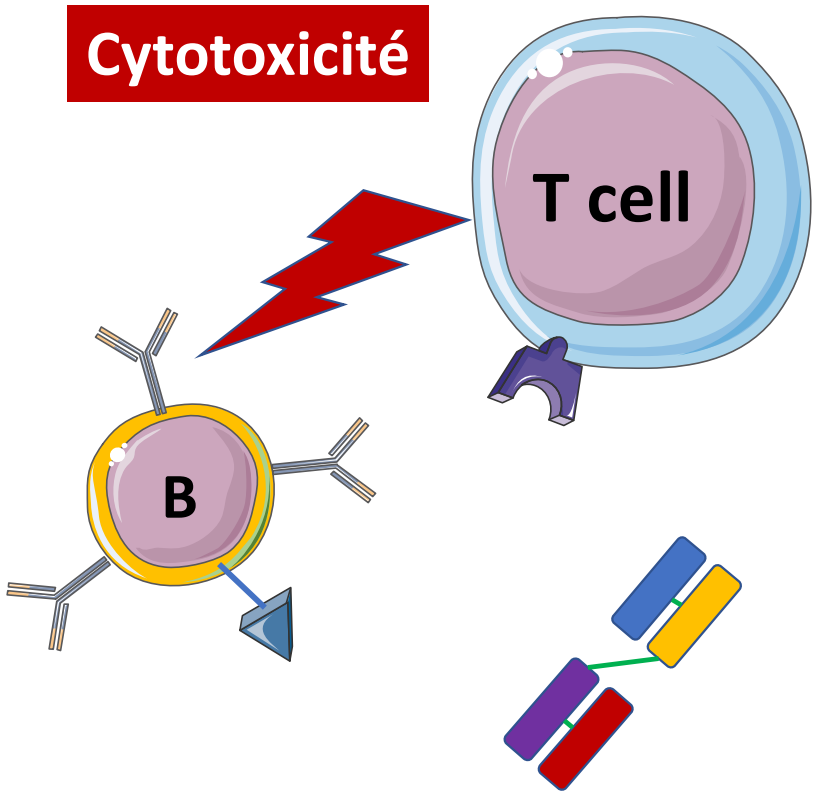
Les limites des CAR-T anti-CD19 autologues

- Leur prix !
- La lourdeur logistique de leur préparation
- Leurs effets secondaires
  - Immunodépression
  - CRS *Cytokine Release Syndrome*
  - ICANs *Immune Effector Cell-Associated Neurotoxicity Syndrome*
  - Lymphomes/leucémies de clones CAR-T ?

Les T cell engagers : une alternative aux CAR-T?

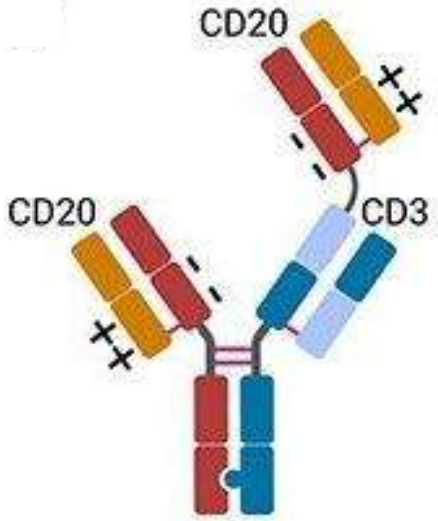
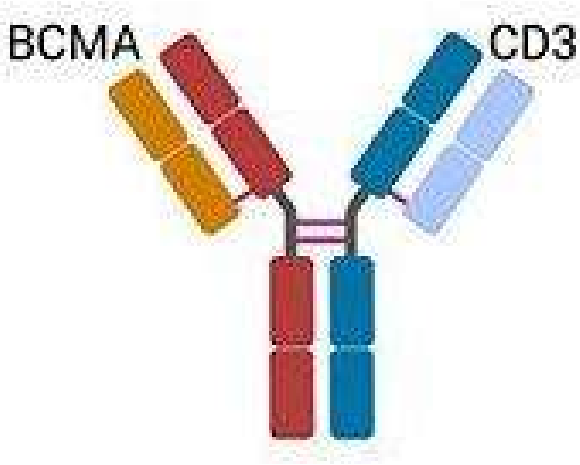


CAR-T cell



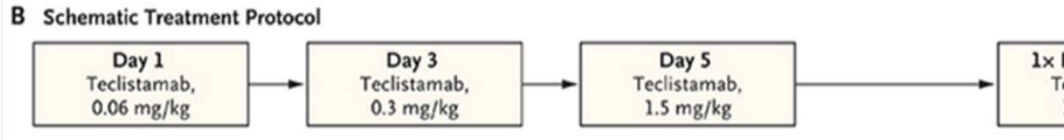
T-cell engagers (TCE)

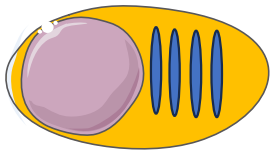
Les T cell engagers en hématologie

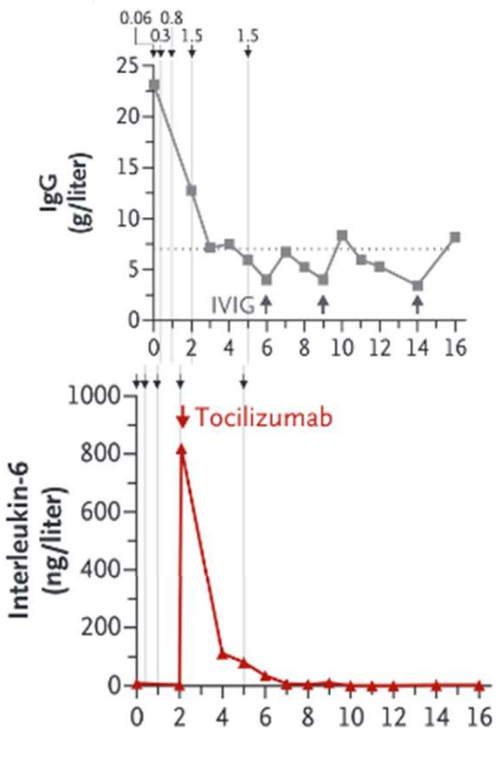
CD19 : B / plasmablastes	CD20 : Lympho B	BCMA => Plasmocytes
		
Blinatumomab	**Glofitamab**	**Teclistamab**
AMM : LAL B	Accès précoce : LDGC B	AMM : myélome 3ème ligne

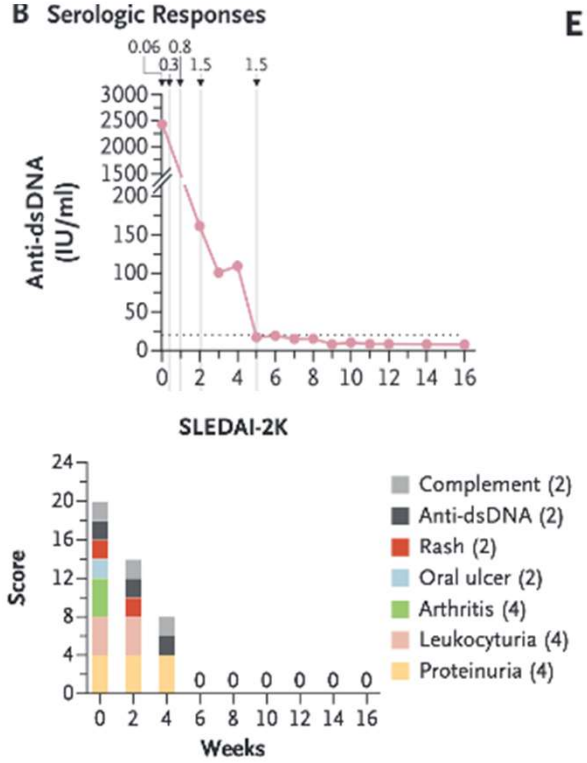
Cibler le plasmoyte avec le Téclistamab

Une patiente de 23 ans avec lupus systémique multiréfractaire









E Changes in Serum Autoantibodies at Latest Follow-up

	Autoantibody	Baseline	Follow-up
Patient 1 (systemic sclerosis)	ANA — titer	1:3200	1:100
	PM-Scl-75 — RU (normal <15)	30	1
	PM-Scl-100 — RU (normal <15)	35	3
Patient 2 (primary Sjögren's syndrome)	ANA — titer	1:10,000	1:3200
	SS-A/Ro-52 — U/ml (normal <25)	129.7	55.3
	SS-A/Ro-60 — U/ml (normal <25)	189.5	131.3
	SS-B/La — U/ml (normal <25)	222.5	165.2
	PL-7 — RU (normal <15)	122	91
Patient 3 (idiopathic inflammatory myositis)	ANA — U/ml (normal <25)	1:100	1:100
	MDA5 — RU (normal <15)	38	18
	RF — U/ml (normal <25)	507.2	18.4
Patient 4 (rheumatoid arthritis)	CCP2 — U/ml (normal <25)	2.7	0.9
	MCV — U/ml (normal <25)	82.9	3.0

Treat-to-target biologique : traiter jusqu'à négativation de l'Auto-anticorps ?

Alexander T et al., N Engl J Med 2024;391(9):864-866.
Hagen M et al., N Engl J Med 2024;391:867-869

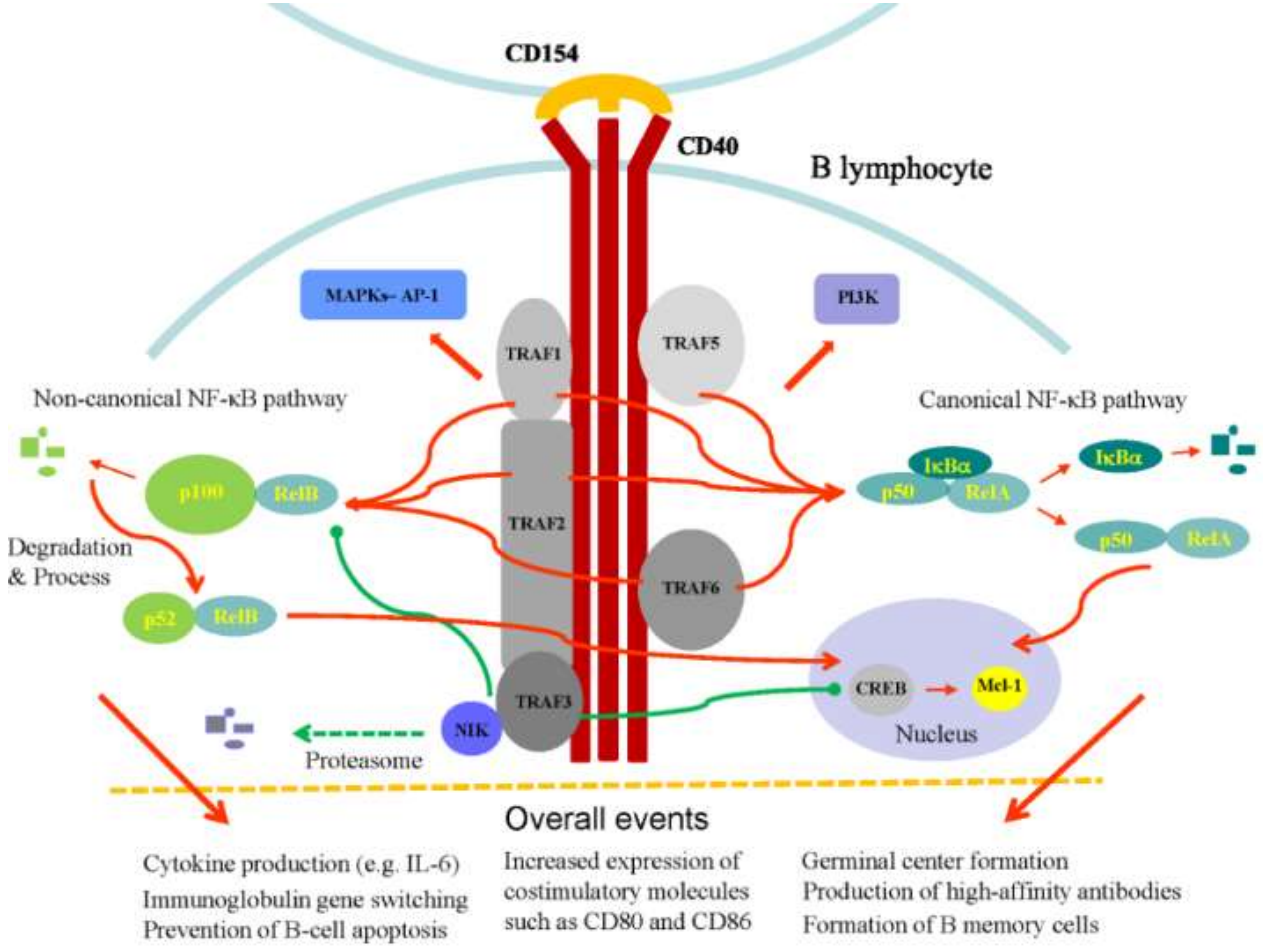
Agenda

- Pourquoi cibler les LB ?

- Comment cibler les LB ?
  - En les détruisant ? *Déplétion, faut-il aller plus profond ?*
  - En les modulant ? *Cibler la coactivation*
  - En éliminant les anticorps ? *Et notamment les autoanticorps*
  - En détruisant seulement les méchants ? *Le phantasme des thérapies ciblant les clones auto-réactifs*
  - En les rééduquant ? *Le phantasme de la vaccination par l'autoantigène*

- Où cibler les LB en France ?
  - La création du C3I

CD 40 inhibition



Lai JH, cells 2019

CD 40 inhibition in Sjögren

Dazodalibep (DAZ), a nonantibody fusion protein that acts as a CD40L antagonist, blocks costimulatory signals between T and B cells and antigen-presenting cells, including epithelial cells

©Horizon Therapeutics plc

Dazodalibep: cohort 1:
ESSDAI
N=74

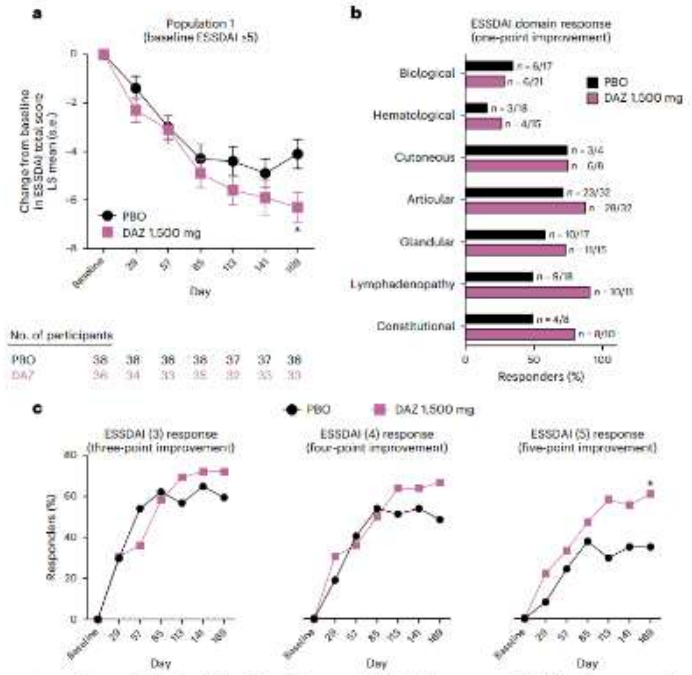


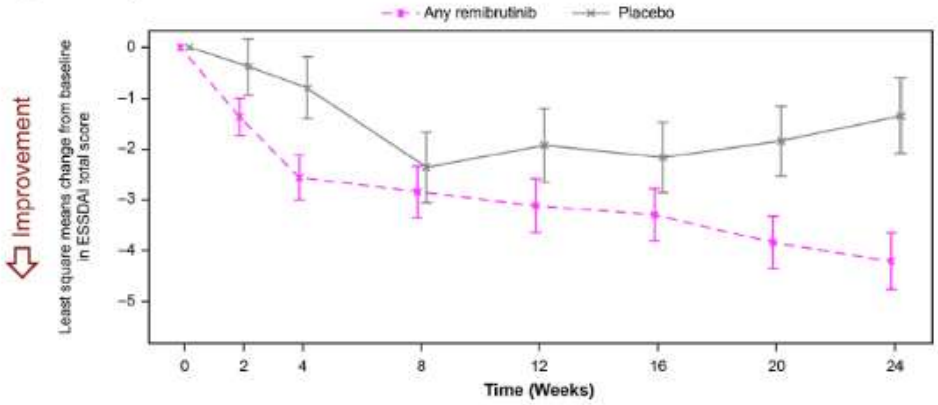
Fig. 2 | ESSDAI treatment outcomes in population 1 consisting of participants with moderate-to-severe systemic disease activity at baseline. **a**–**c**, Population 1 ESSDAI scores. **a**, Total score plotted by study visit and analyzed by MMRM (day 169, $P = 0.0167$, two-sided t-test). **b**, ESSDAI domain response summarized descriptively. Only participants with baseline involvement are included in the summary. **c**, ESSDAI total score responders at thresholds of three-, four- and five-point improvement from baseline (ESSDAI (5) response was a post hoc analysis) analyzed by logistic regression. P values were not adjusted for multiplicity; $^*P < 0.05$.

Positive randomized phase 2b (dose ranging, n=273)

St Clair, Nature Med, 2024

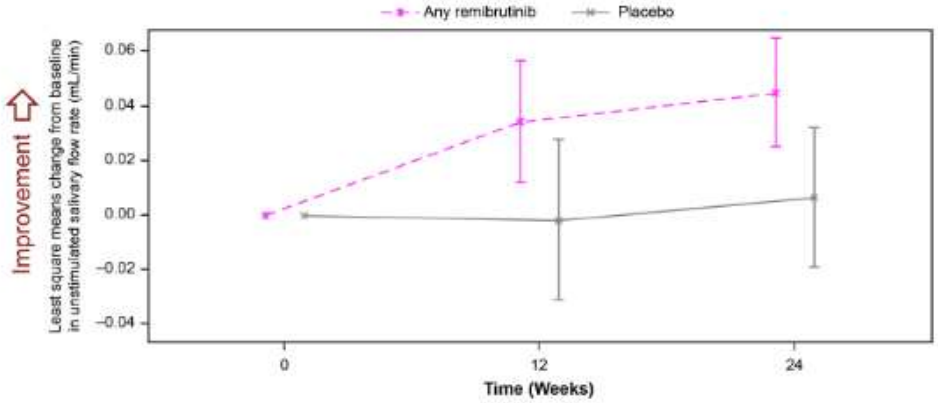
BTK inhibition in Sjögren

Figure 1. Change from baseline in ESSDAI total score over 24 weeks



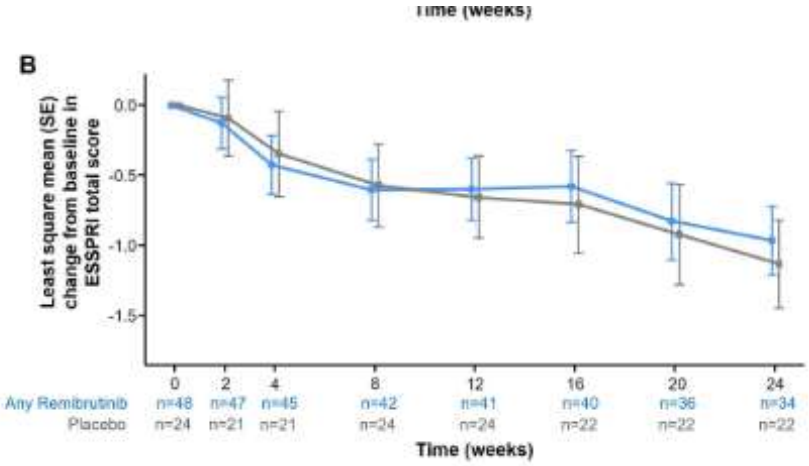
Mixed effect model for repeated measurements; least square mean (standard error)
ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; EULAR, European Alliance of Associations for Rheumatology

Figure 2. Change from baseline in unstimulated salivary flow over 24 weeks



Mixed effect model for repeated measurements; least square mean (standard error)

Remibrutinib



Dorner T et al. ARD, 2024

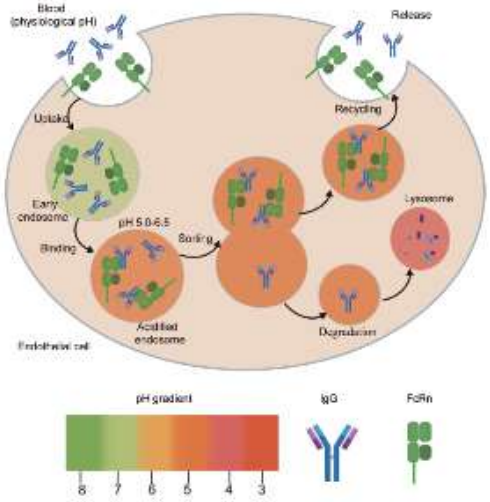
Agenda

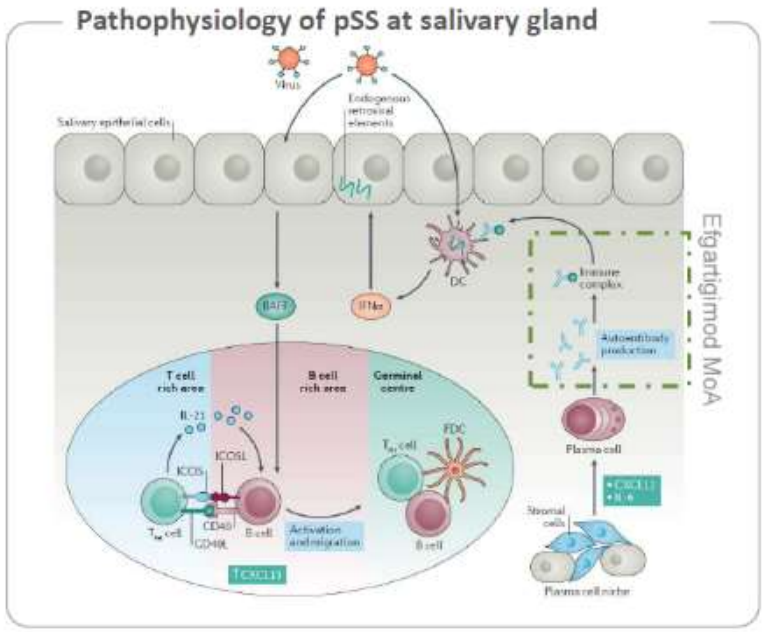
- Pourquoi cibler les LB ?

- Comment cibler les LB ?
  - En les détruisant ? *Déplétion, faut-il aller plus profond ?*
  - En les modulant ? *Cibler la coactivation*
  - En éliminant les anticorps ? *Et notamment les autoanticorps*
  - En détruisant seulement les méchants ? *Le phantasme des thérapies ciblant les clones auto-réactifs*
  - En les rééduquant ? *Le phantasme de la vaccination par l'autoantigène*

- Où cibler les LB en France ?
  - La création du C3I

FcRn inhibition





Nipocalimab in Sjögren

Phase II positive (n=150)
Recent Sjogren
ESSDAI> 5
CRESS
Phase III: DAFFODIL

Zuh LN, Neural regen research, 2022
EULAR 2024 - LBA0010, Gottenberg JE et al

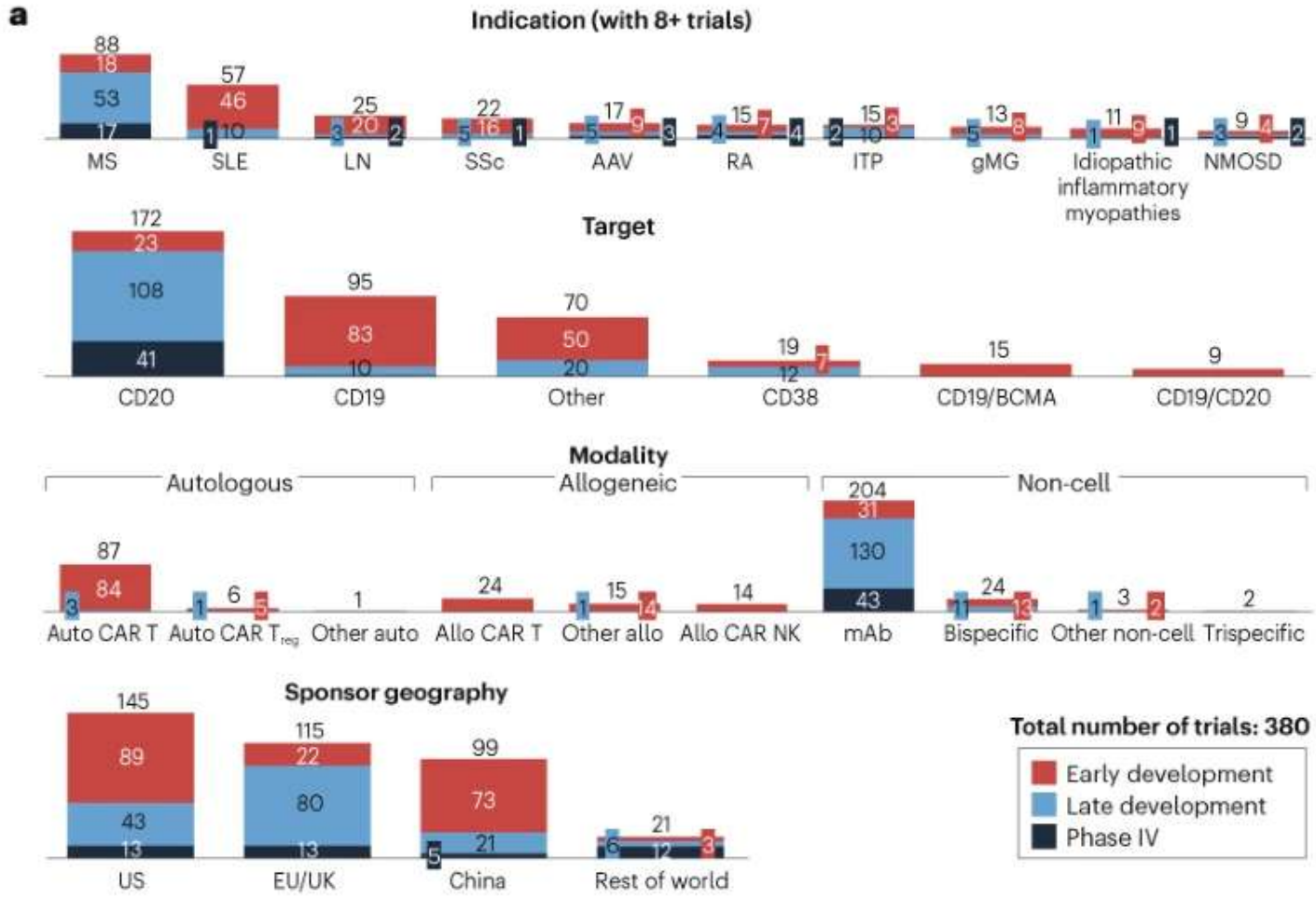
Ulrichts P, et al. J Clin Invest 2018
Broome CM, Lancet 2023
EULAR 2024 - LBA0010, Gottenberg JE et al

Où en est-on aujourd’hui ?

FROM THE ANALYST'S COUCH | 12 May 2025

The race to reset autoimmune diseases

By Mayank Bhandari, Jeff Smith, Emily Capra & Guang Yang



Agenda

- Pourquoi cibler les LB ?

- Comment cibler les LB ?
  - En les détruisant ? *Déplétion, faut-il aller plus profond ?*
  - En les modulant ? *Cibler la coactivation/la signalisation des LB*
  - En éliminant les anticorps ? *Et notamment les autoanticorps*
  - En détruisant seulement les méchants ? *Le phantasme des thérapies ciblant les clones auto-réactifs*
  - En les rééduquant ? *Le phantasme de la vaccination par l'autoantigène*

- Où cibler les LB en France ?

Club immunothérapies intensives dans les IMIDs

- **Groupe pluridisciplinaire**
- **National**
- **Structuration par le biais d'une association**

- **<u>Objectifs:</u>**

➔ **Promouvoir l'utilisation d'immunothérapies intensives dans les IMIDs**

- ➢ **Clinique : essais et hors essais**
- ➢ **Recherche fondamentale et translationnelle**
- ➢ **Formation des professionnels de santés**

➔ **Structuration d'un reseau national en lien avec FAI2R**

Comité de direction

Jérome AVOUAC
Rhumatologue
Président

Marc SCHERLINGER
Rhumatologue
Vice président

Gaétane NOCTURNE
Rhumatologue
Trésorière

Benjamin TERRIER
Interniste

Camille BIGENWALD
Hématologue

Maurine JOURET
Pédiatre
Secrétaire

David LAUNAY
Interniste

Noémie JOURDE-CHICHE
Néphrologue

Comité de pilotage

Jean SIBILIA
Rhumatologue

Xavier MARIETTE
Rhumatologue

Alexandre BELOT
Pédiatre

Divi CORNEC
Rhumatologue

Raphaele SEROR
rhumatologue

Justine DECROOCQ
Hématologue

Olivier HERMINE
Hématologue

Cristina CASTILLA-LLORENTE

Christian JORGENSEN
Rhumatologue

Christophe RICHEZ
Rhumatologue

Marie-Elise TRUCHETET
Rhumatologue

Alain MEYER
Rhumatologue

Laurent PEYRIN-BIROULET
Gastro-entérologue

Thierry MARTIN
Immunologue

Zahir AMOURA
Interniste

Nathalie COSTEDOAT
Interniste

Membres des groupes de travaux

Grégory PUGNET
Interniste

Emmanuel DONNADIEU
Scientifique

Samuel BITOUN
Interniste

Membres des groupes de travaux

Julien ZUBER
Néphrologue

Edouard FORCADE
Hématologue

Sylvain CHOQUET
Hématologue

Philippe BOUSSO
Scientifique

Sébastien Viel
Scientifique

FHU - IMPACT

IMmuno-intervention et PAthologies inflammatoires Chroniques – Territoire HUGO

Co Portage – CHU de Rennes et Brest

Coordonnateurs: Divi Cornec, Alain Lescoat, Laure Michel

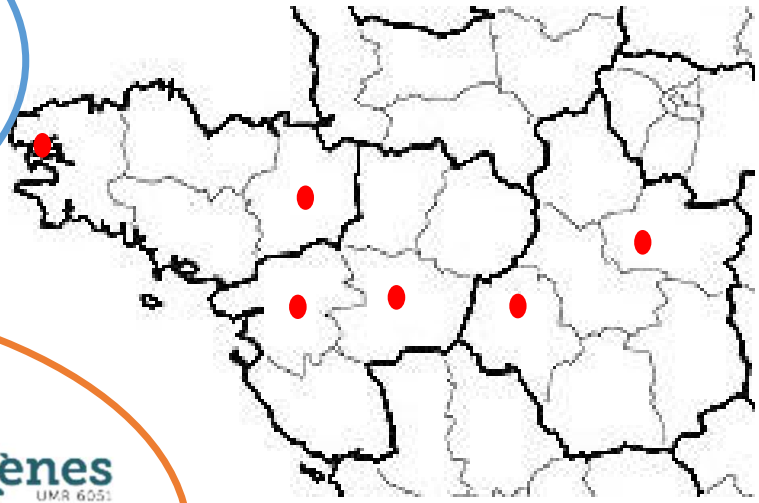
FHU impact

Contexte

Forces & périmètre

Projet

- Immunologie Clinique
- Neurologie
- Pneumologie
- SPATIOMICS Immunomonitoring



- Immunologie Clinique

- Immunologie Clinique
- Neurologie
- Pneumologie

- Immunologie Clinique
- Neurologie
- Pneumologie
- SITI Immunomonitoring

- Immunologie Clinique
- Neurologie

- Immunologie Clinique
- Neurologie
- Pneumologie

FHU impact

Au delà de HUGO : Participation de Lucie Biard, Méthodologie, APHP