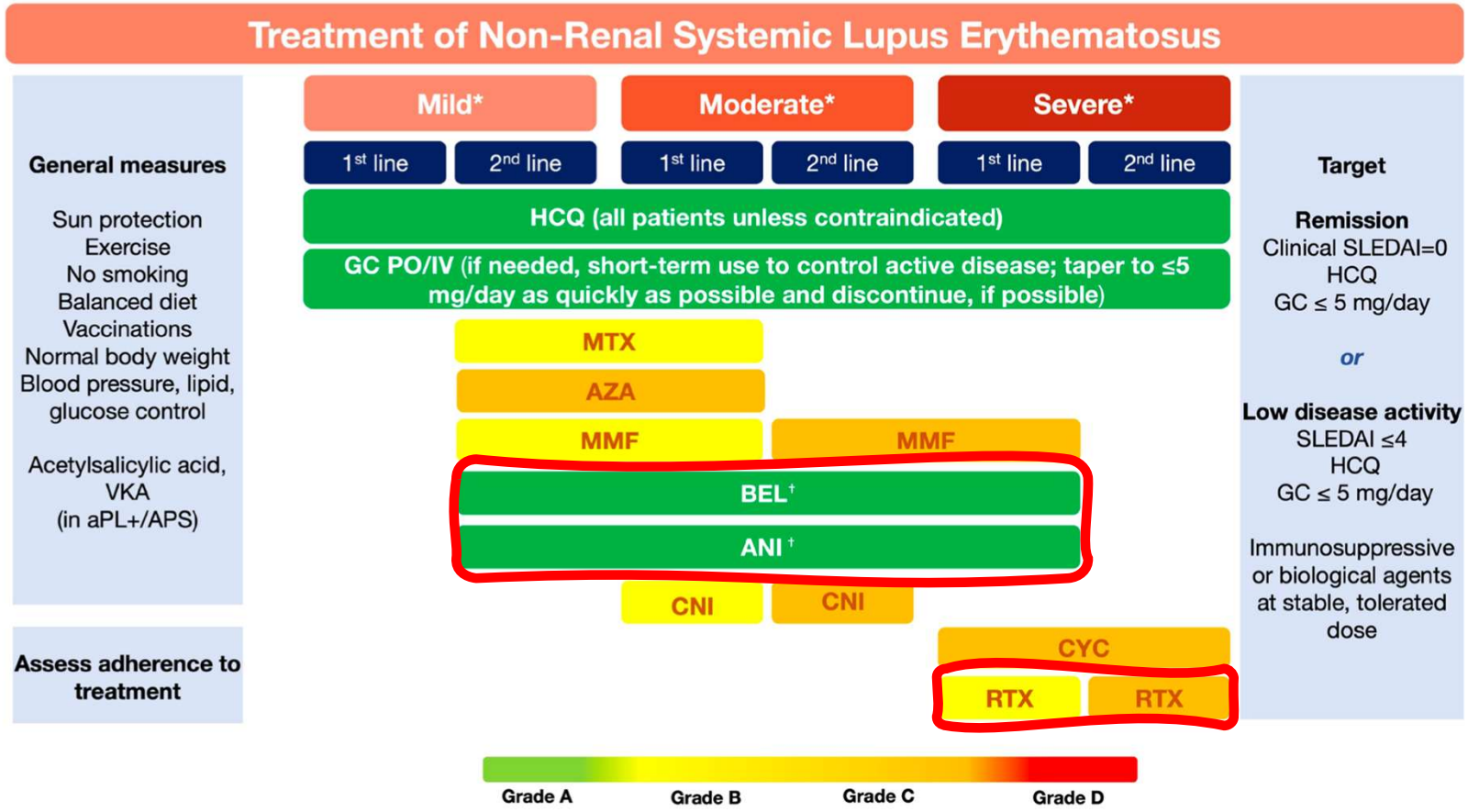
Traitements ciblés dans le lupus systémique

Christophe Richez,
CHU de Bordeaux
https://www.reso-bordeaux.fr

Liens d’intérêt C Richez

- Aide à la recherche (dans le cadre de PHRC) : Biogen, Lilly et Nordic Pharma
- Interventions ponctuelles et expertise : Abbvie, Alpha Sigma, Amgen, Astra Zeneca, Biogen, Boehringer, BMS, Celltrion, GSK, Lilly, MSD, Novartis, Sandoz et Pfizer
- Participations bordelaises à plusieurs essais CAR-T (Novartis & BMS actuellement)

EULAR recommendations for the management of systemic lupus erythematosus: 2023 update



Fanouriakis A, *et al*. *Ann Rheum Dis* 2023

Nouvelles recommandations EULAR 2023

- Hydroxychloroquine (HCQ) en 1ère ligne : pas de changement avec toujours la dose de 5 mg/kg/j !

- **Corticoïdes** : diminution de la dose cible à **≤ 5 mg/j** ; arrêt si possible ; possibilité de bolus IV

- Stratégies d'épargne en corticoïdes : **utilisation précoce des DMARDs/IS ou biomédicaments afin de réduire la dose de corticoïdes.** Pas de nécessité d'utiliser un DMARD/IS en 1er
  - *In patients not responding to HCQ, or patients unable to reduce GCs below doses acceptable for chronic use, addition of immunomodulating/ immunosuppressive agents (for MTX, AZA, MMF and/or biologic agents: belimumab or anifrolumab) should be considered.*

Fanouriakis A, *et al*. *Ann Rheum Dis* 2023

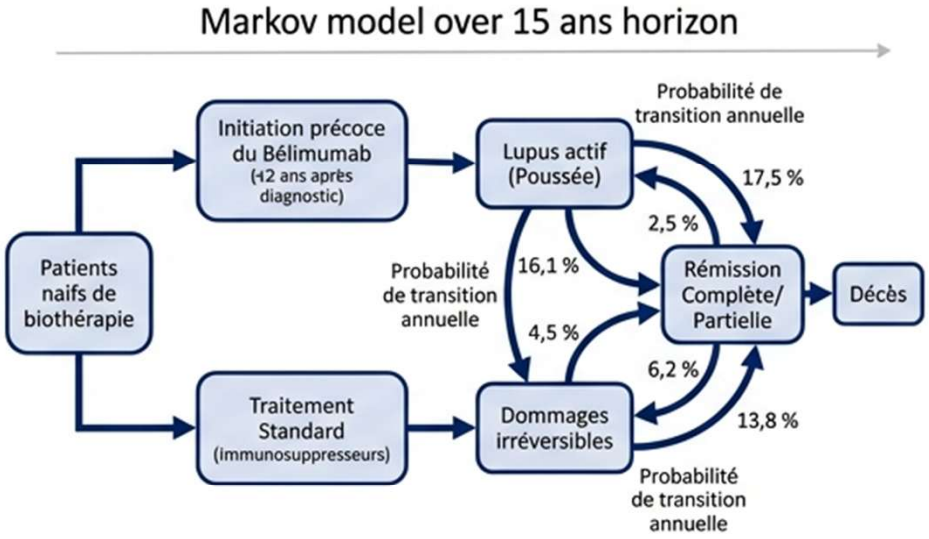
Les biomédicaments peuvent permettre une réduction des corticoïdes

- Confirmation de l'efficacité du belimumab dans le LES extrarénal (revue systématique Cochrane, étude observationnelle)
- Anifrolumab approuvé après les essais TULIP.
- Le belimumab et l'anifrolumab ont une meilleure efficacité que le placebo chez les patients ayant des marqueurs sérologiques d'activité (C3/C4 et/ou anti-ADN).
- **Utilisation des DMARDs/IS (MTX, AZA, MMF, leflunomide…) non obligatoire avec une biothérapie**

Fanouriakis A, *et al*. *Ann Rheum Dis* 2023

Le bélimumab précoce redéfinit la trajectoire de la maladie

Rationnel & Design



Comparaison de l'initiation précoce (<2 ans après diagnostic) vs l'initiation retardée (après échec des immunosuppresseurs standards) chez des patients naïfs de biothérapie.

Population

- Cohorte modélisée : 1000 patients
- Âge moyen : 41 ans
- Proportion de femmes : 91,2 %
- Score SLEDAI-2K > 0

Résultats & Conclusion

+0,95
Gain de QALYs par patient

-$126 337
Économies médicales directes par patient

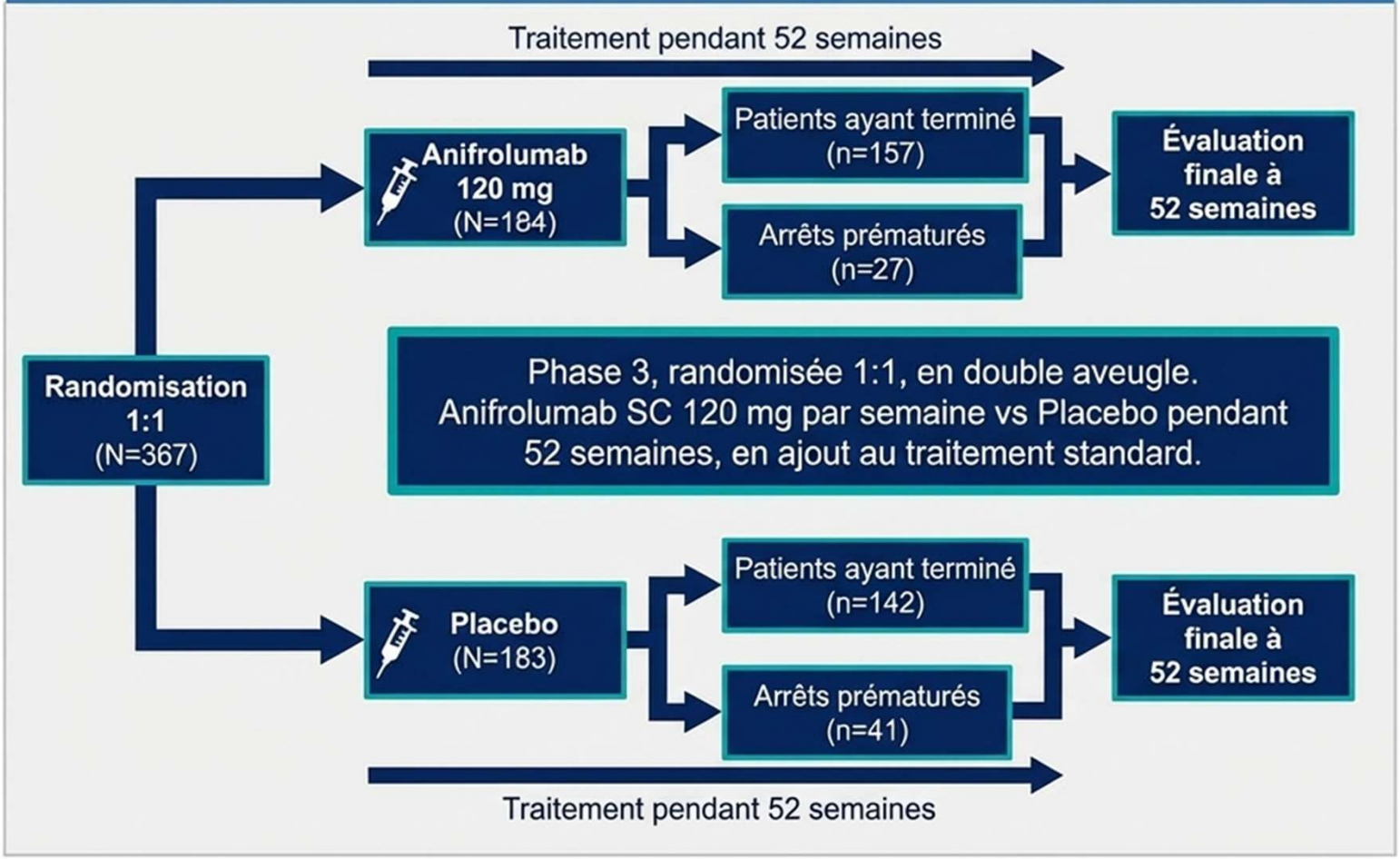
L'initiation précoce améliore les résultats cliniques tout en réduisant drastiquement les coûts, justifiant une réévaluation des critères de remboursement actuels.

Généré par IA

Hundal S, et al. JAMA Network Open. 2026

Anifrolumab SC : essai TULIP-SC

Design de l'étude



Population à l'inclusion

N total : **367 patients**
(184 Anifrolumab, 183 Placebo)

Âge moyen : **42,5 ans**

Score SLEDAI-2K moyen : **10,8**

Patients avec SLEDAI-2K ≥ 10 : **67,3 %**

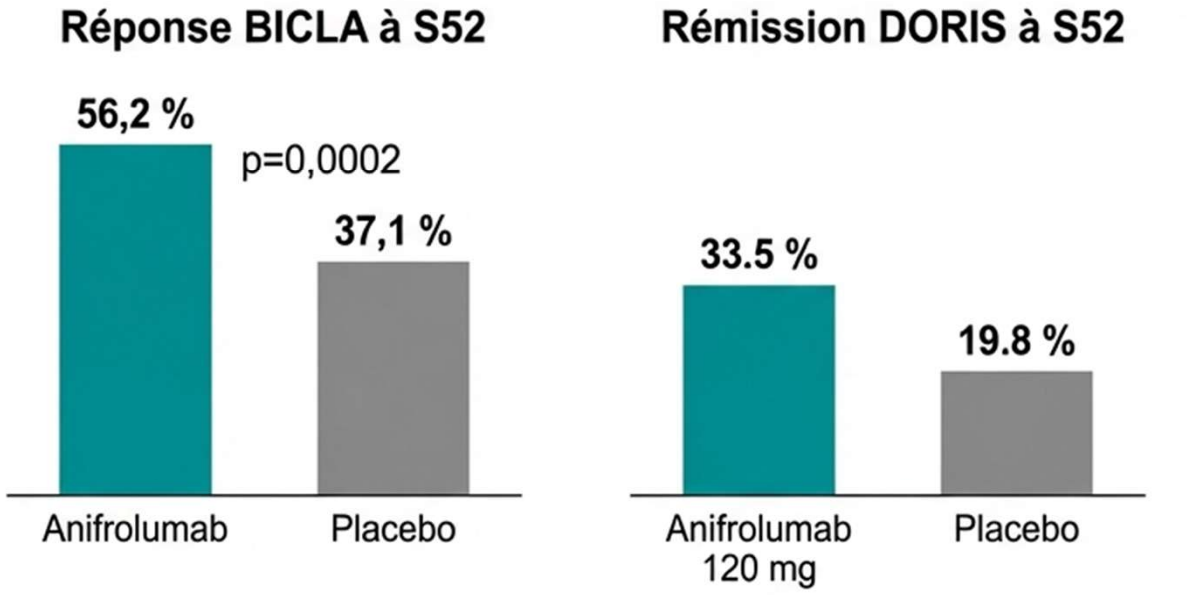
Patients sous immunosuppresseurs : **54,8 %**

Généré par IA

Manzi S, et al. A&R 2026

L’anifrolumab SC démontre une efficacité clinique > au PBO

Efficacité Principale & Secondaire



Réduction soutenue des glucocorticoïdes :
56,2 % (Anifrolumab) vs 34,0 % (Placebo).

Tolérance

Profil globalement bien toléré.

Infections des voies respiratoires supérieures (22,2 % vs 18,7 %).

Zona (Herpes zoster) : 3,8 % vs 1,1 %.

Conclusion

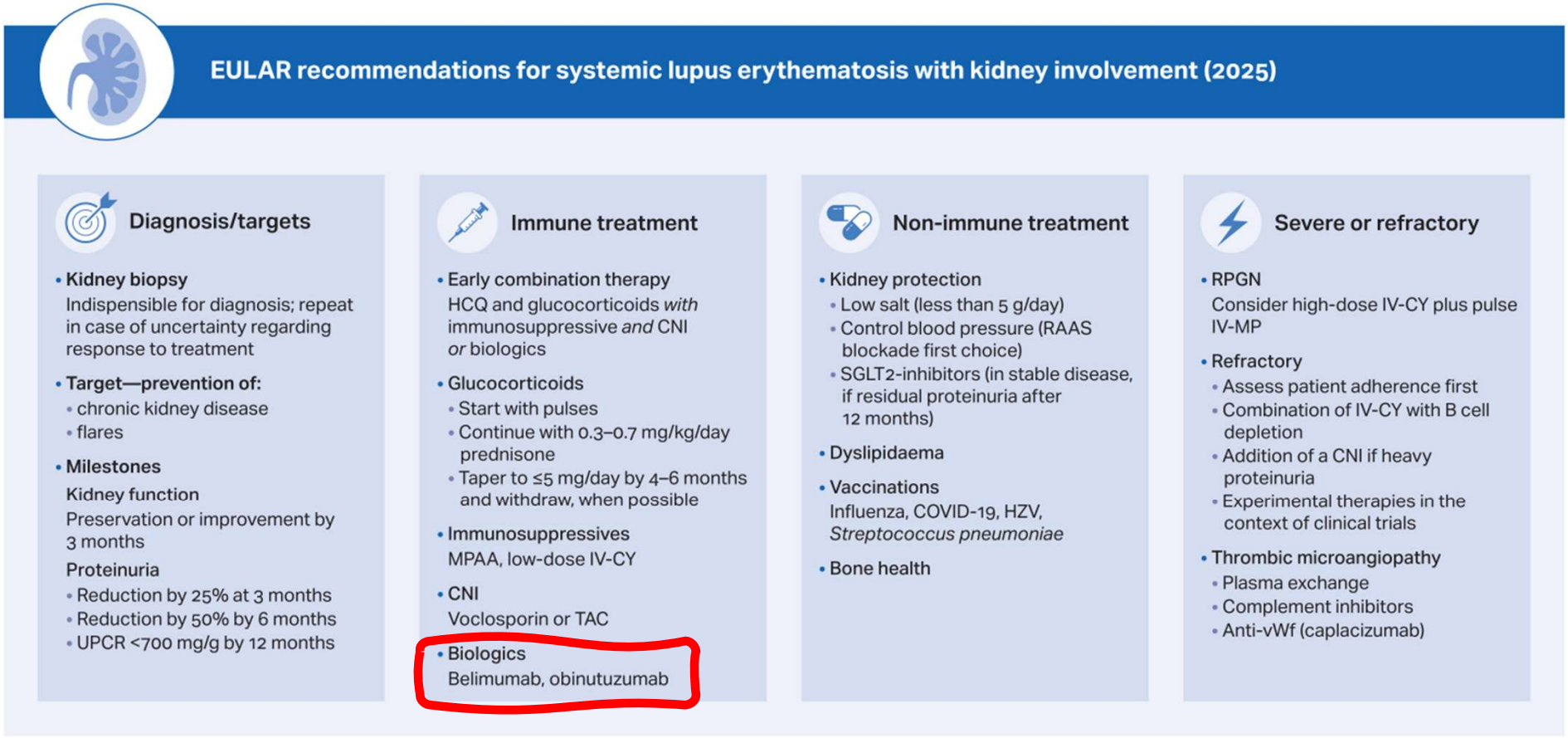
La voie sous-cutanée hebdomadaire offre des bénéfices cliniques significatifs (BICLA, épargne cortisonique, rémission DORIS) avec un profil de sécurité comparable à la formulation intraveineuse, facilitant l’accès au traitement.

Généré par IA

Manzi S, et al. A&R 2026

Recommendations

EULAR recommendations for the management of systemic lupus erythematosus with kidney involvement: 2025 update



Fanouriakis A, *et al*. *Ann Rheum Dis* 2026

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 17, 2025 VOL. 392 NO. 15

Efficacy and Safety of Obinutuzumab in Active Lupus Nephritis

R.A. Furie,[1] B.H. Rovin,[2] J.P. Garg,[3] M.B. Santiago,[4-6] G. Aroca-Martínez,[7,8] A.E. Zuta Santillán,[9] D. Alvarez,[10] C. Navarro Sandoval,[11] A.M. Lila,[12] J.A. Tumlin,[13] A. Saxena,[14] F. Irazoque Palazuelos,[15] H. Raghu,[3] B. Yoo,[3] I. Hassan,[16] E. Martins,[17] H. Sehgal,[17] P. Kirchner,[17] J. Ross Terres,[3] T.A. Omachi,[3] T. Schindler,[17] W.F. Pendergraft III,[3] and A. Malvar,[18] for the REGENCY Trial Investigators*

ABSTRACT

BACKGROUND

Obinutuzumab, a humanized type II anti-CD20 monoclonal antibody, provided significantly better renal responses than placebo in a phase 2 trial involving patients with lupus nephritis receiving standard therapy.

METHODS

In a phase 3, randomized, controlled trial, we assigned adults with biopsy-proven active lupus nephritis in a 1:1 ratio to receive obinutuzumab in one of two dose schedules (1000 mg on day 1 and at weeks 2, 24, 26, and 52, with or without a dose at week 50) or placebo. All patients received standard therapy with mycophenolate mofetil, along with oral prednisone at a target dose of 7.5 mg per day by week 12 and 5 mg per day by week 24. The primary end point was a complete renal response at week 76, defined by a urinary protein-to-creatinine ratio of less than 0.5 (with protein and creatinine both measured in milligrams), an estimated glomerular filtration rate of at least 85% of the baseline value, and no intercurrent event (i.e., rescue therapy, treatment failure, death, or early trial withdrawal). Key secondary end points at week 76 included a complete renal response with a prednisone dose of 7.5 mg per day or lower between weeks 64 and 76 and a urinary protein-to-creatinine ratio lower than 0.8 without an intercurrent event.

RESULTS

A total of 271 patients underwent randomization; 135 were assigned to the obinutuzumab group (combined dose schedules) and 136 to the placebo group. A complete renal response at week 76 was observed in 46.4% of the patients in the obinutuzumab group and 33.1% of those in the placebo group (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 2.0 to 24.8; P=0.02). A complete renal response at week 76 with a prednisone dose of 7.5 mg per day or lower between weeks 64 and 76 was observed in more patients in the obinutuzumab group than in the placebo group (42.7% vs. 30.9%; adjusted difference, 11.9 percentage points; 95% CI, 0.6 to 23.2; P=0.04), and a urinary protein-to-creatinine ratio lower than 0.8 without an intercurrent event was more common with obinutuzumab than with placebo (55.5% vs. 41.9%; adjusted difference, 13.7 percentage points; 95% CI, 2.0 to 25.4; P=0.02). No unexpected safety signals were identified. More serious adverse events, mainly infections and events related to coronavirus disease 2019, occurred with obinutuzumab than with placebo.

CONCLUSIONS

Among adults with active lupus nephritis, obinutuzumab plus standard therapy was more efficacious than standard therapy alone in providing a complete renal response. (Funded by F. Hoffmann–La Roche; REGENCY ClinicalTrials.gov number, NCT04221477.)

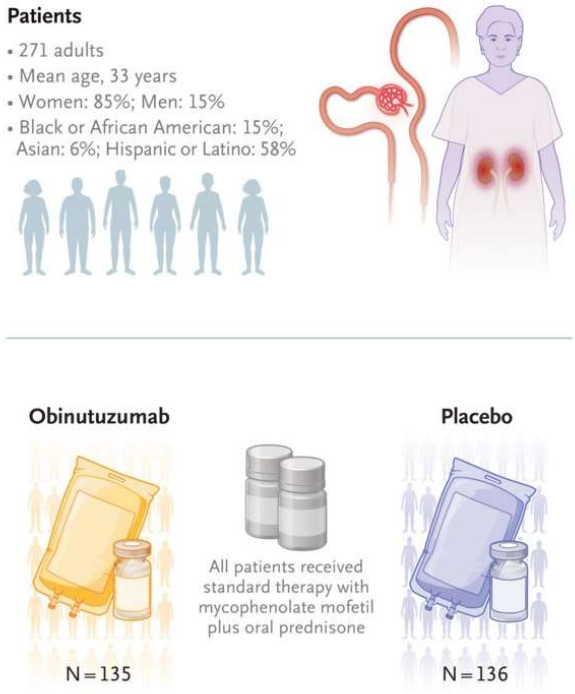
The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Furie can be contacted at rfurie@northwell.edu or at the Division of Rheumatology, Northwell Health, Donald and Barbara Zucker School of Medicine at Hofstra–Northwell, 865 Northern Blvd., Suite 302, Great Neck, NY 11021.

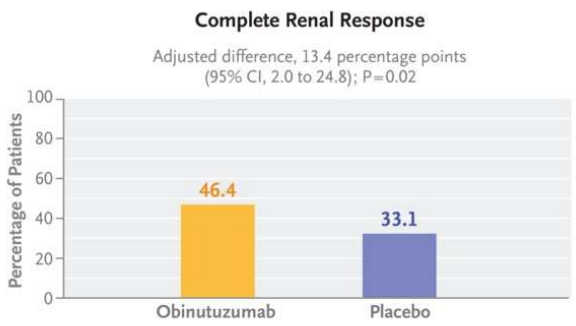
*A list of investigators in the REGENCY trial is provided in the Supplementary Appendix, available at NEJM.org.

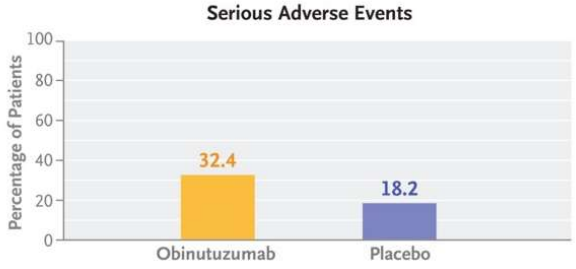
This article was published on February 7, 2025, at NEJM.org.

N Engl J Med 2025;392:1471-83.
DOI: 10.1056/NEJMoa2410965

CME







The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Obinutuzumab in Active Systemic Lupus Erythematosus

R.A. Furie,[1,2] M. Dall'Era,[3] E.M. Vital,[4,5] J.P. Garg,[6] F. Irazoque Palazuelos,[7] A.E. Zuta Santillán,[8] J. Ravelo-Hernández,[9] M.B. Santiago,[10-12] B. Zazueta Montiel,[13] S. Botha,[14] P. Leszczyński,[15] V.A. de Souza,[16] S.A. Sicsik,[17] L. Bellatin,[18] A. Naidoo,[19] Z. Amoura,[20] M.A. D'Agostino,[21,22] S. Kumar,[23] B. Workeneh,[24] J. Rae,[6] H.A. Mao,[25] F. Erblang,[26] O. Meier,[26] J.C. Maller,[6] and A.D. Askanase,[27] for the ALLEGORY Trial Investigators[a]

ABSTRACT

BACKGROUND

Obinutuzumab, a glycoengineered type II anti-CD20 monoclonal antibody, induces potent B-cell depletion and is approved for the treatment of active lupus nephritis. Its efficacy and safety in patients with active systemic lupus erythematosus (SLE) are yet to be determined.

METHODS

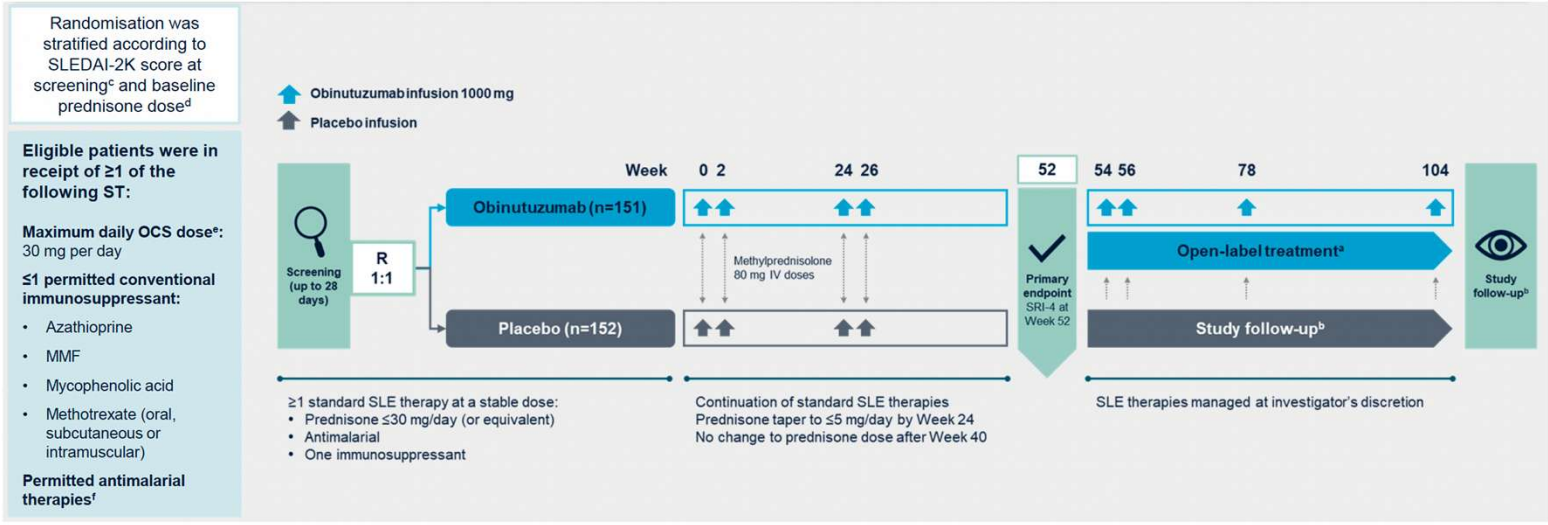
We conducted a phase 3, multicenter, double-blind, placebo-controlled trial involving adults with active SLE but without proliferative or membranous lupus nephritis who were receiving standard therapy. Patients were randomly assigned in a 1:1 ratio to receive obinutuzumab (1000 mg) or placebo on day 1 and weeks 2, 24, and 26. In the prespecified analysis, the primary end point at week 52 was a response on the SLE Responder Index 4 (SRI-4), defined by a reduction from baseline of at least 4 points in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, no worsening of disease as assessed by the British Isles Lupus Assessment Group (BILAG) 2004 index and Physician's Global Assessment, and no intercurrent events (i.e., major concomitant-therapy violation, receipt of rescue medication, or early discontinuation of trial participation due to death, lack of efficacy, or adverse events).

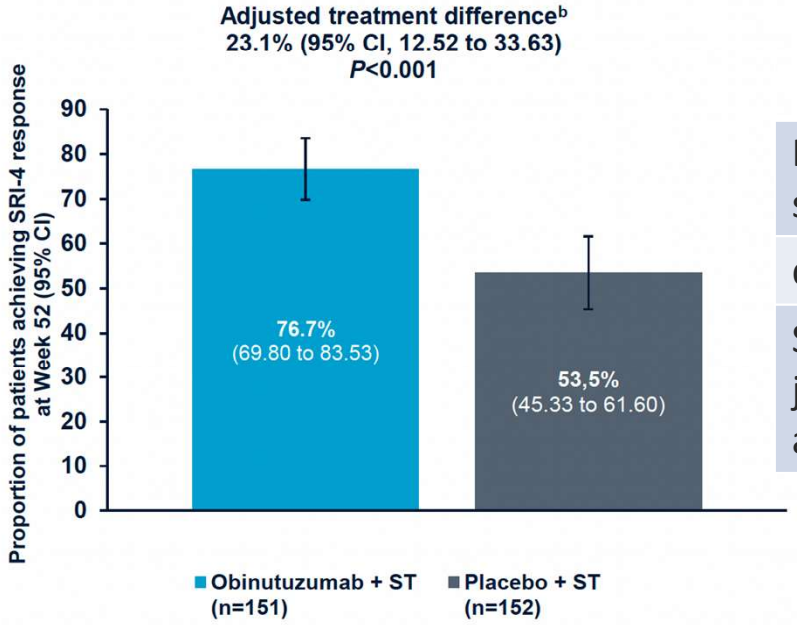
RESULTS

Of 303 patients who underwent randomization, 151 were assigned to receive obinutuzumab and 152 to receive placebo. At week 52, an SRI-4 response was observed in 76.7% of the patients in the obinutuzumab group and in 53.5% of those in the placebo group (adjusted difference, 23.1 percentage points; 95% confidence interval [CI], 12.5 to 33.6; P<0.001). In an additional analysis whereby nonfatal intercurrent events did not affect response status, the respective percentages were 85.4% and 68.5% (adjusted difference, 16.8 percentage points; 95% CI, 7.1 to 26.4). Obinutuzumab was superior to placebo with respect to all key secondary end points: BILAG-based Composite Lupus Assessment response, sustained reduction in glucocorticoid dose, sustained SRI-4 response, SRI-6 response, and time to first BILAG-defined flare. Adverse events were reported in 88.7% of the patients in the obinutuzumab group and in 81.5% of those in the placebo group, and serious adverse events in 15.9% and 11.9%, respectively. One patient in the obinutuzumab group and 3 in the placebo group died during the double-blind period.

CONCLUSIONS

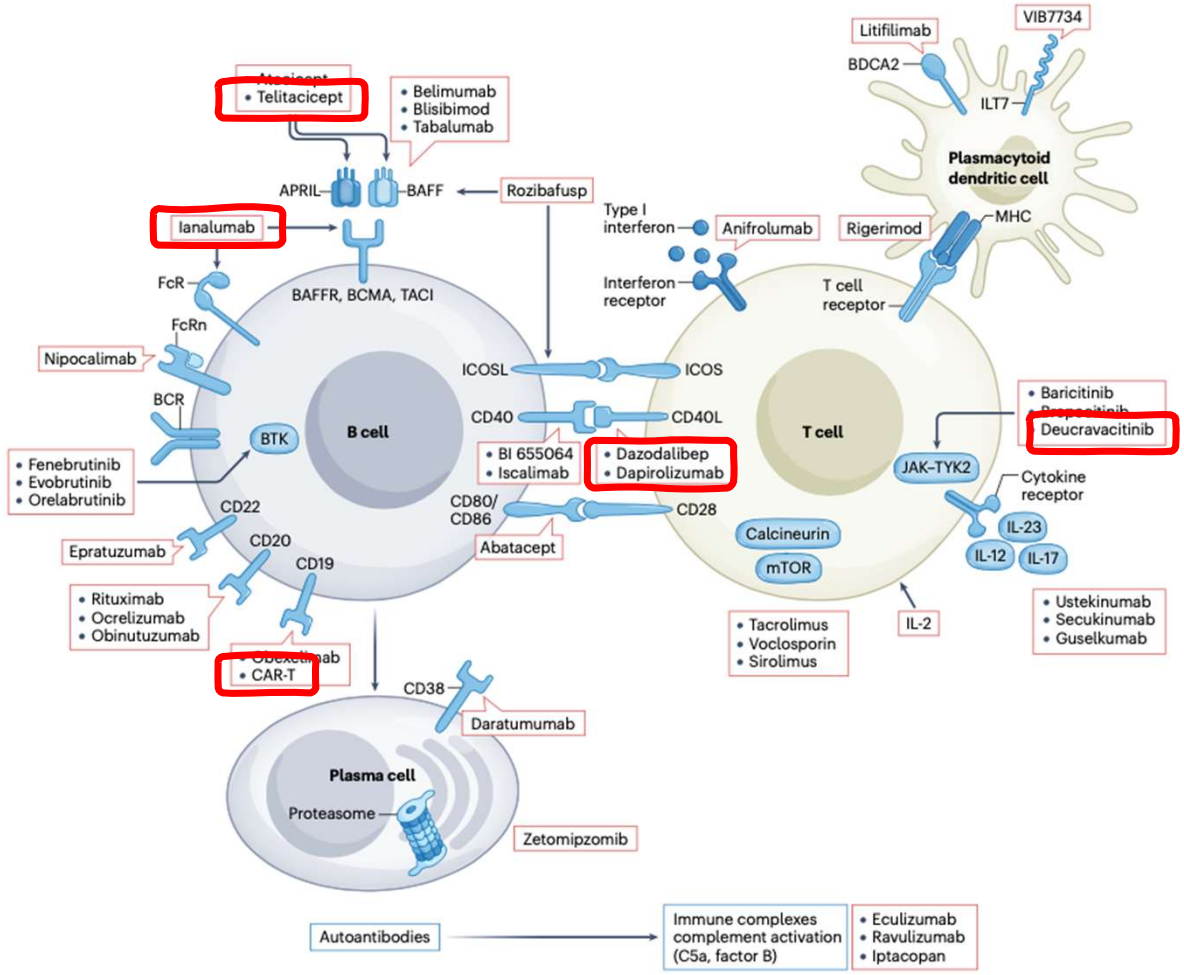
Among adults with active SLE, treatment with obinutuzumab was superior to placebo with respect to the primary and all key secondary end points. (Funded by F. Hoffmann–La Roche; ALLEGORY ClinicalTrials.gov number, NCT04963296.)





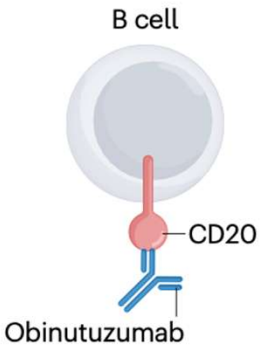
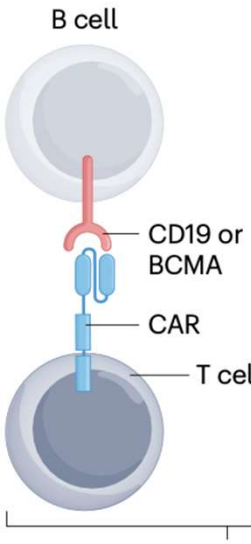
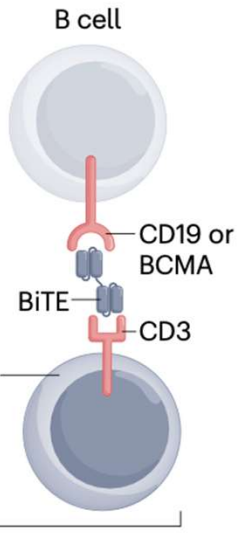
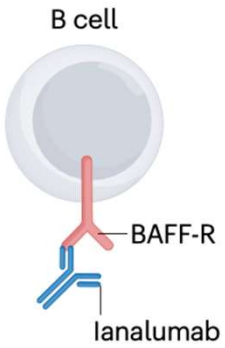
	OBI (n=151)	PBO (n=151)
Infections sévères	8,6%	4,6%
décès	0,7%	3,3%
SAE justifiant arrêt	2%	2%

Quels sont les traitements possiblement disponibles à court terme (ou en hors-AMM) ?



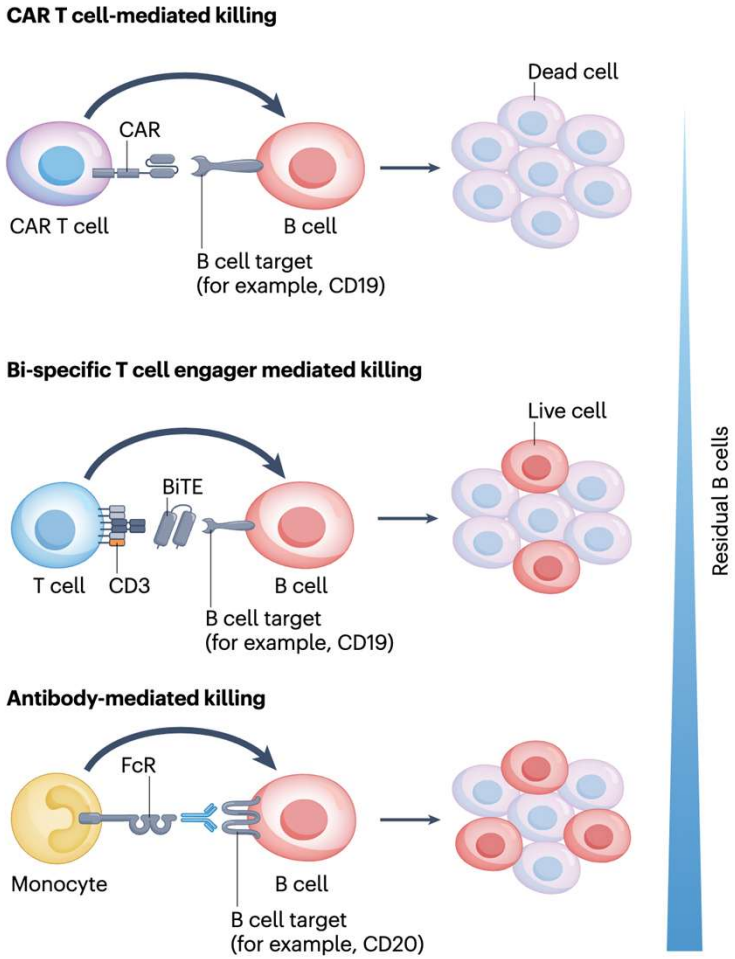
Mok CC, et al. Nat Rev Rheumatol. 2023 Mar 2.

La déplétion lymphocytaire B

	Deep depletion			Reduced relapse of B cell numbers
Mode of action	**Obinutuzumab**	**CAR T cell**	**BiTE**	**Ianalumab**
				
Improvements compared with rituximab	• Humanized to reduce immunogenicity • Afucosylated Fc region to improve FcγRIII affinity • Improved direct cytotoxicity to B cells	• Targeting CD19 or BCMA, that are more broadly expressed compared to CD20 • Potentially improved depletion by engagement of T cells		• Fully human to reduce immunogenicity • Afucosylated Fc region to improve FcγRIII affinity • BAFF-R inhibition

Stockfelt M, et al. Nat Rev Rheumatol. 2025 Jan 15

L’avenir nous dira quel est le meilleur moyen de se débarrasser des lymphocytes B



nature medicine

Article

https://doi.org/10.1038/s41591-024-02964-1

Bispecific T cell engager therapy for refractory rheumatoid arthritis

Received: 13 December 2023

Accepted: 1 April 2024

Published online: 26 April 2024

Check for updates

Laura Bucci[1,2,7], Melanie Hagen[1,2,7], Tobias Rothe[1,2], Maria Gabriella Raimondo[1,2], Filippo Fagni[1,2], Carlo Tur[1,3], Andreas Wirsching[1,2], Jochen Wacker[1,2], Artur Wilhelm[1,4], Jean-Philippe Auger[1,2], Milena Pachowsky[1,2], Markus Eckstein[5], Stefano Alivernini[3], Angelo Zoli[3], Gerhard Krönke[1,4], Stefan Uderhardt[1,2], Aline Bozec[1,2], Maria-Antonietta D’Agostino[3], Georg Schett[1,2,3,6,8] & Ricardo Grieshaber-Bouyer[1,2,8]

LYMPHOID NEOPLASIA

Comment on Kim et al, page 629

CARs vs bispecifics: the race is on!

Tanya Siddiqi | City of Hope Orange County

Schett G, et al. Nat Rev Rheumatol. 2024 Sep;20(9):531-544.

Association bélimumab + rituximab = la solution ?

- Efficacité suggérée dans l'étude en ouvert SYNBIOSE

Kraaij T, et al. J Autoimmun 2018;91:45-54.

- Plus discutable dans la néphrite lupique réfractaire de CALIBRATE

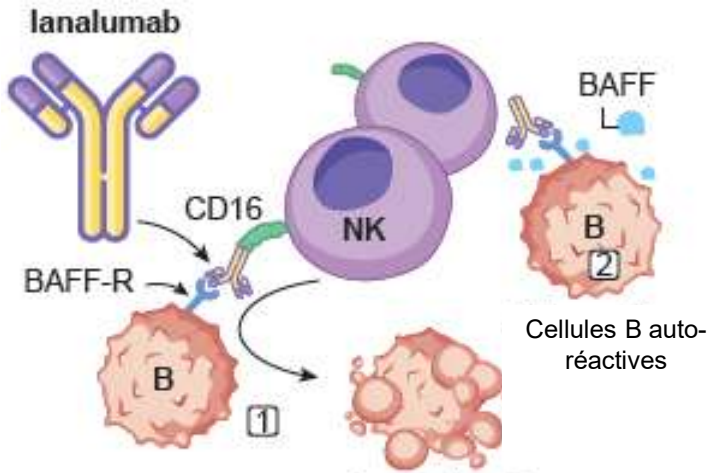
Atisha-Fregoso Y, et al. Arthritis Rheumatol 2021;73(1):121-131

- Données BEAT-LUPUS sur 52 patients
  - Béli après le ritux vs sans béli
  - 10 poussées sévères vs 3

Ehrenstein M et al., abstr. OP0129

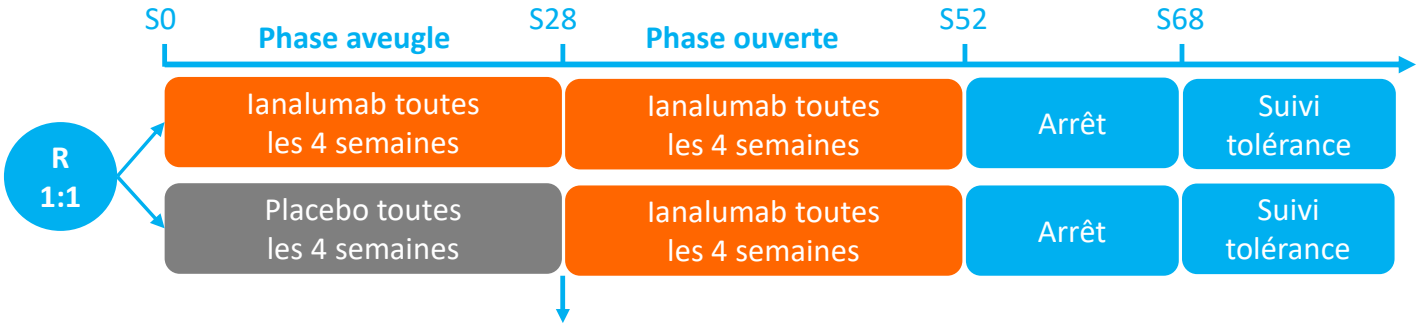
- Débuter le béli avant le ritux > Etudié dans le SGS

Ianalumab dans le lupus systémique



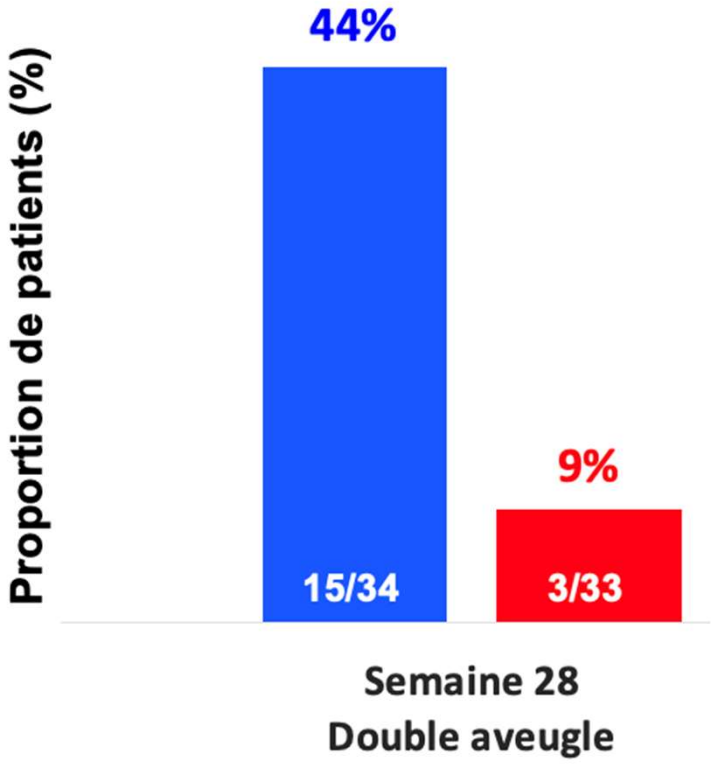
Cellules B auto-réactives

Promotion de la mort des cellules B



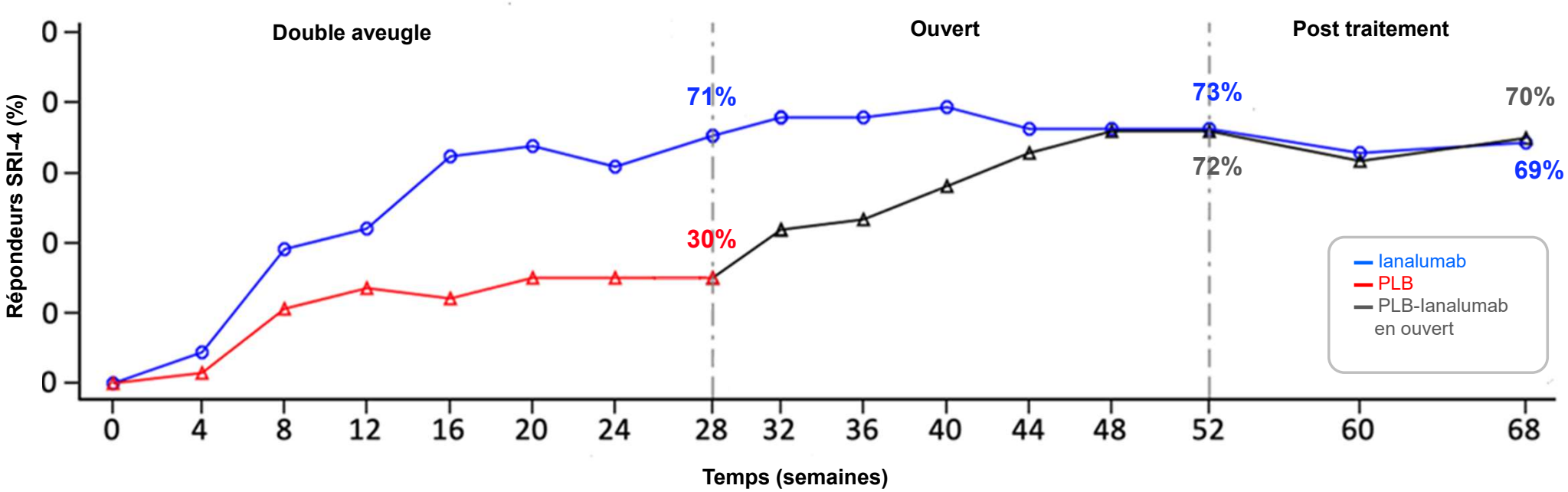
Critère principal S28

- Réponse SRI-4
- ET prednisone ≤ 5 mg maintenu de S16 à S28



Agmon-Levin *et al. ARD 2024;*83(supp1):140-141

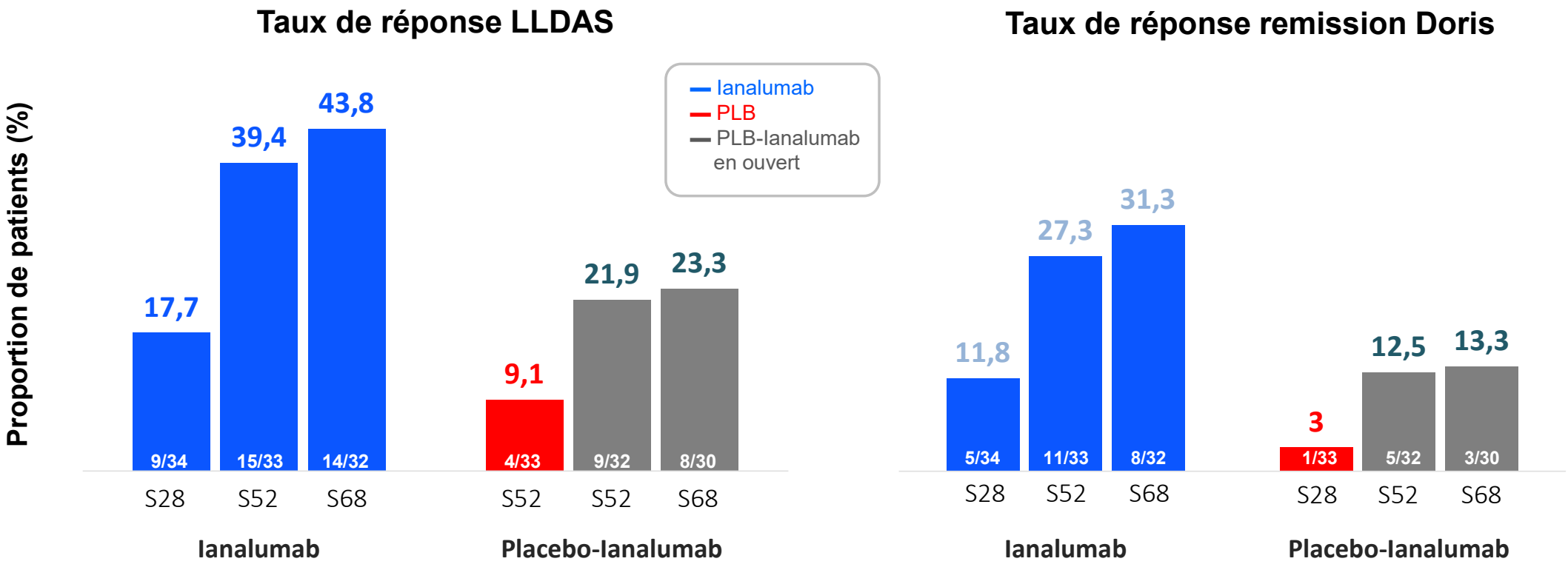
Ianalumab dans le lupus systémique



- Le traitement par Ianalumab a été bien toléré jusqu'à la S52, sans apparition de nouveaux signaux entre la S28 et la S52

Agmon-Levin *et al. ARD 2024;*83(supp1):140-141

Ianalumab dans le lupus systémique



- Le traitement par Ianalumab a été bien toléré jusqu'à la S52, sans apparition de nouveaux signaux entre la S28 et la S52

Agmon-Levin *et al. ARD 2024;*83(supp1):140-141

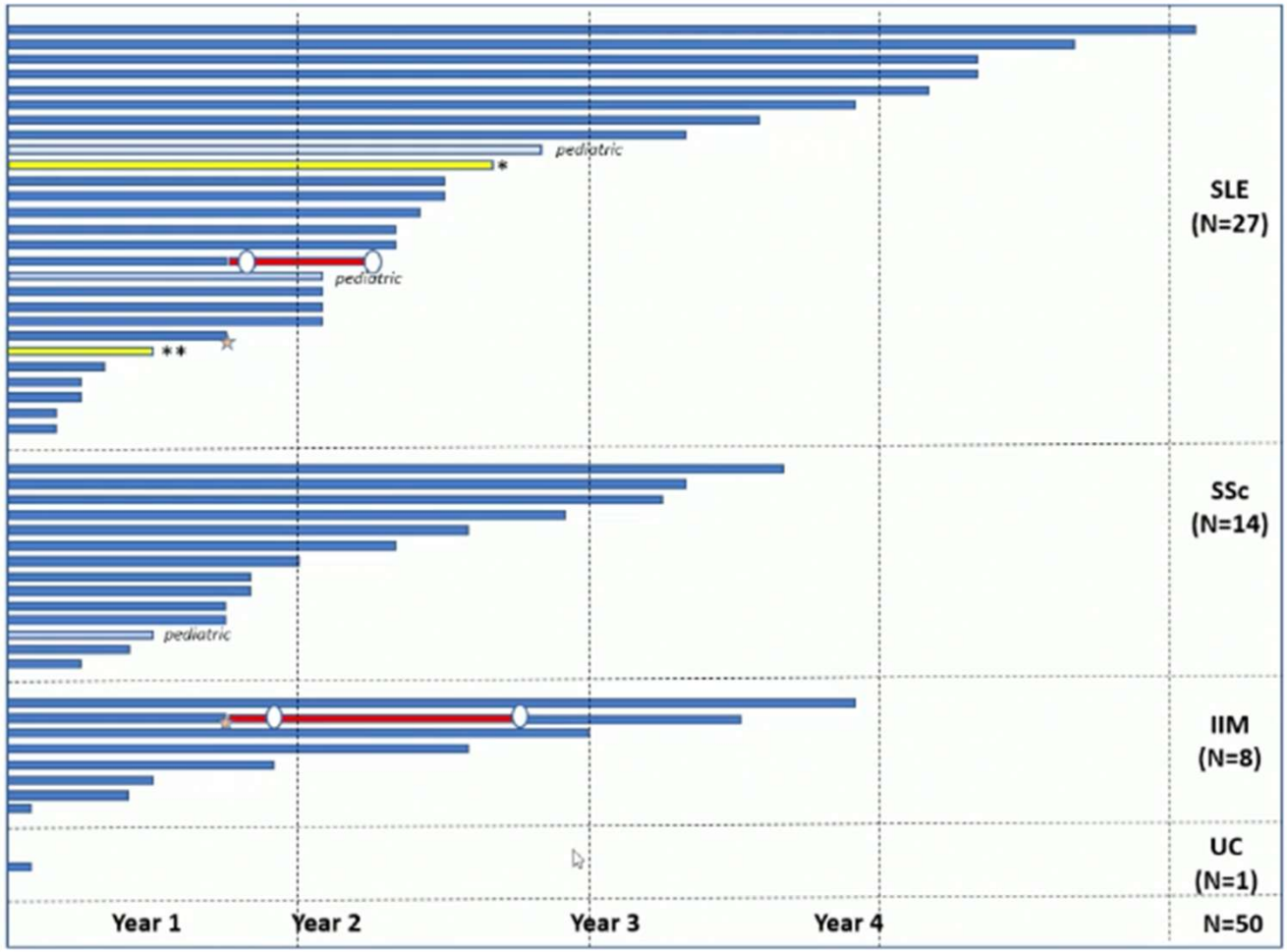
Quelles sont les données disponibles actuellement ?

	Lupus systémique						
	Schett G[1]	Morand E[2]	Sheikh S[3]	Wu C[4]	Wang W[5]	Kong R[6]	Schett G[7]
Cible	CD19	CD19	CD19	CD19/BCMA	CD19/BCMA	CD19	CD19
n	27	21	8	10	13	26	11
Produit	Miltenyi CAR-T	Novartis CAR-T	Cabaletta Bio CAR-T	GC012F (AZD0120) FasTCAR-T	iCell Gene CAR-T	Riu Therapeutics Allo NK	BMS CAR-T
Efficacité	96% DORIS M12 1 rechute	Pas d'activité, malgré arrêt des traitements ; Obtention pour la plupart d'une rémission DORIS dès 3 mois				8/12 DORIS 9/12 LLDAS À 12 mois	↘ SLEDAI médian de 10 pts ; ∅ ttt
Tolérance	68% CRS1, 1 CRS2, 0 ICAN	12 CRS1/2, 1 ICAN4	2 CRS1, 1 ICAN4	7 CRS1/2, 0 ICAN	13 CRS1, 0 ICAN	2 CRS1, 0 ICAN	5 CRS 1, 1 CRS2, 1 ICAN grade 3 ; 1 🤰
Suivi max de 48 mois							

+ de nombreux case reports

[1]Schett G et al., EULAR 2025 Bench to bedisde ; [2]Morand et al. EULAR 2025 ; OP0079 ; [3]Sheikh S A et al. EULAR 2025 ; OP0202 ; [4]Wu C et al. EULAR 2025 ; OP0074 ; [5]Wang W, et al. ARD 2024 Sep 30;83(10):1304-1314 ; [6]Kong R, et al. EULAR 2025 ; LB0009 ; [7]Schett G, et al. Arthritis Rheumatol. 2024; 76 (suppl 9)

Donnée CAR-T de l'équipe de Georg Schett



Long-Term Effects in a nutshell

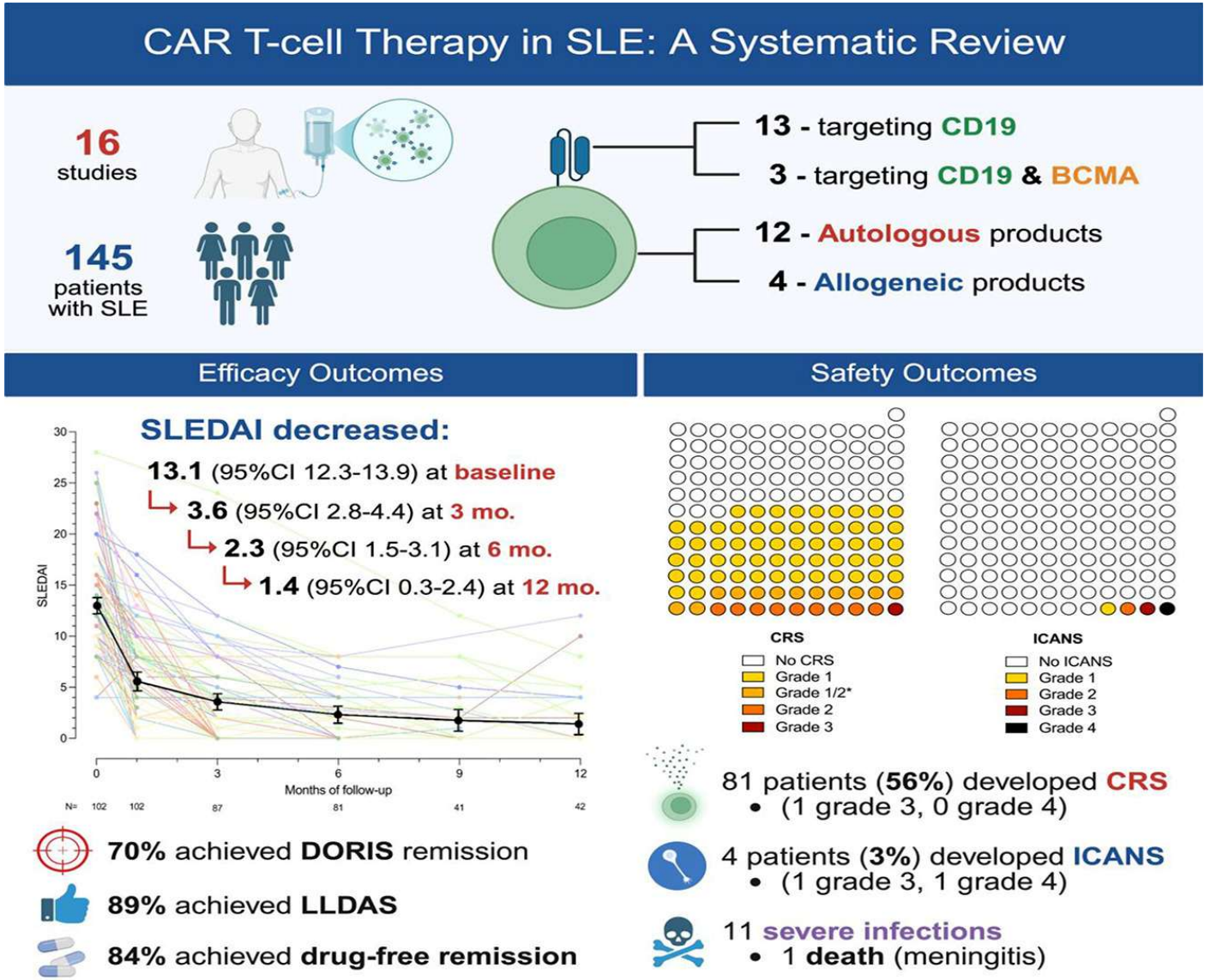
50 patients
72,5 patient years

- 0 deaths
- 2 relapses
- 96% off drugs
- 92% in remission (SLE, IIM) or no progress (SSc)

*SLE:renal damage due to thombotic microangiotahy

**SLE: transverse myelitis (so far not improved)

Schett G. EULAR 2025, bench to bedside

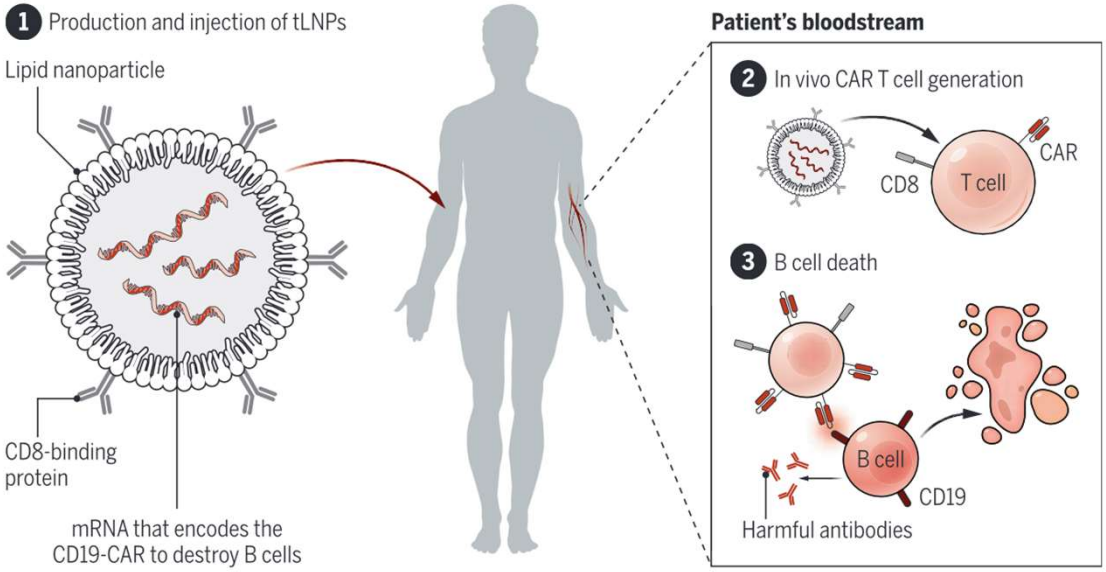


Nordmann-Gomes A, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786

IMMUNOTHERAPY

Engineering immunotherapy from within

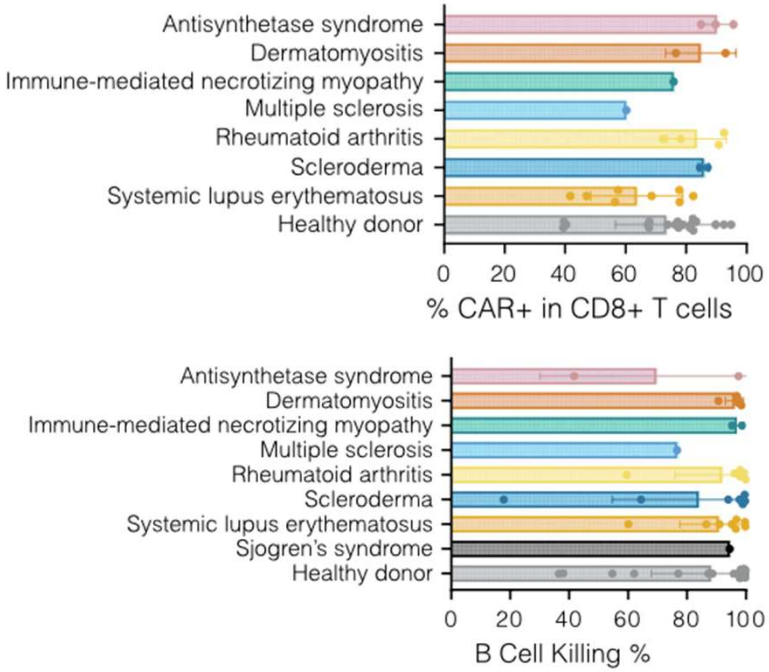
Lipid nanoparticles are designed to generate therapeutic T cells inside living animal models



- distribution hépatique réduite,
- délivrance ciblée aux cellules immunitaires,
- biodégradabilité et tolérance améliorées.

IMMUNOTHERAPY

In vivo CAR T cell generation to treat cancer and autoimmune disease



Hunter TL et al. Science 2025;388(6753):1311-1317
Peche V & Gottschalk. Science 2025;388(6753):1273-1274

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

In Vivo CD19 CAR T-Cell Therapy for Refractory Systemic Lupus Erythematosus

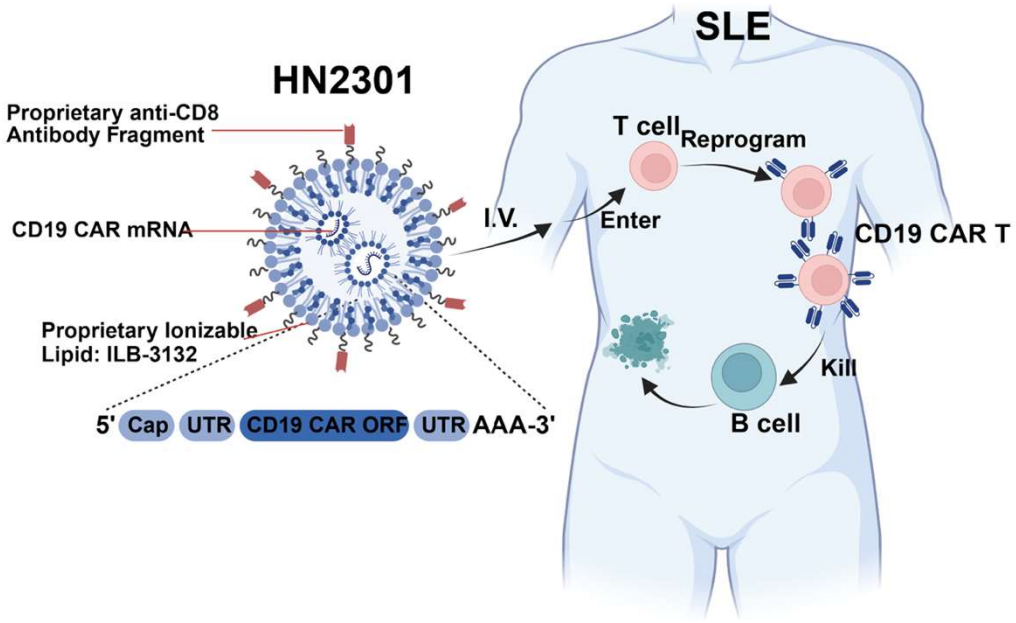
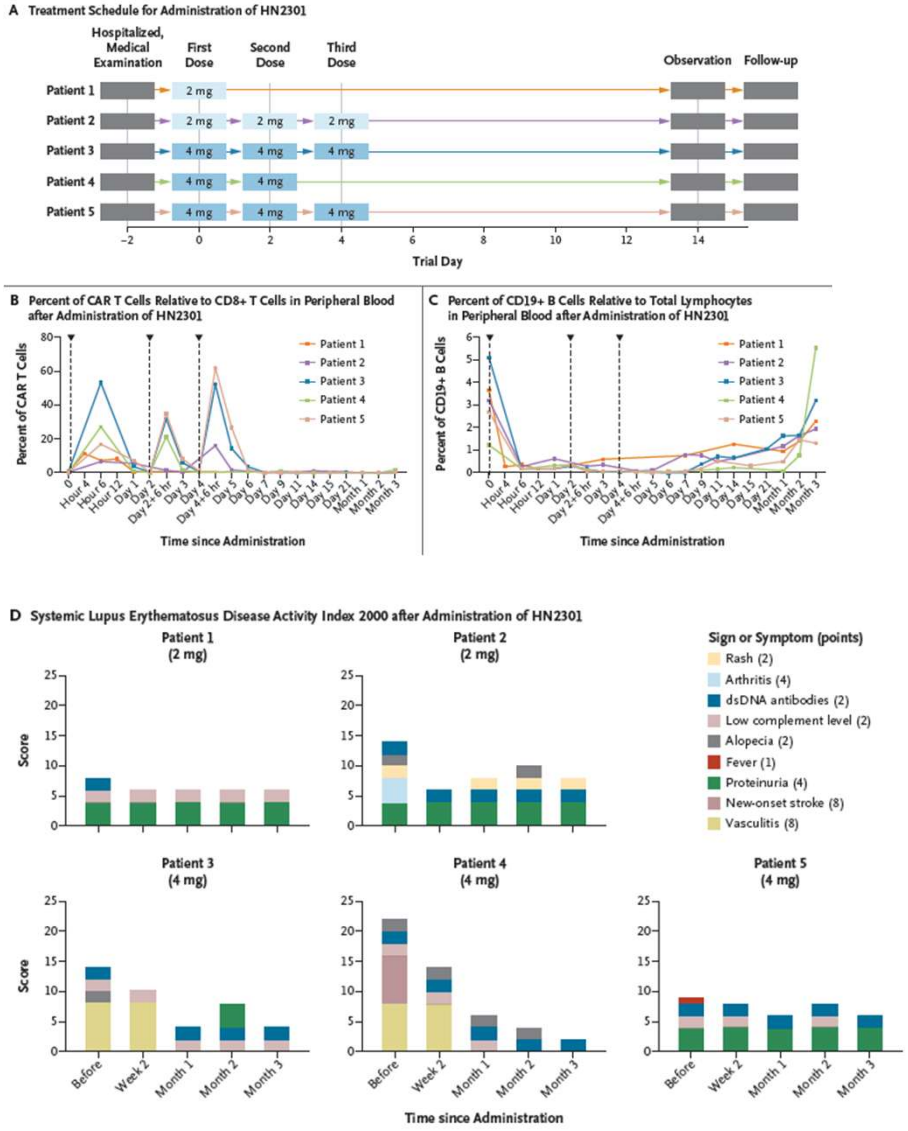


Figure S1. HN2301 schematic diagram and the mechanism of action diagram of HN2301.



Wang Q, et al. NEJM 2025;393:1542-1544

Mais aussi

- **CAR-T CD19 autologues** : Essai basket CASTLE de phase 1/2 incluant 10 LES, 9 sclérodermies systémiques et 5 myopathies inflammatoires. 22/24 patients atteignent les critères de réponse prédéfinis ; bonne tolérance

Müller F, et al. Nat Med 2026 Jan 7

- **CAR-T BCMA autologues** : Essai de phase 1 incluant 7 patients avec NL réfractaire. DORIS rémission chez 5/7 (~71 %), SLEDAI-2K médian tombant à 0 ; bonne tolérance. Biopsies rénales = réduction des CI et de l'inflammation

Hu Z, et al ARD 2025;84(10):1675-1683.

- **CAR-T CD19 + BCMA autologues** : Essai de phase 1 incluant 15 LES réfractaire. À M3, rémission ou LLDAS chez 12/15 patients (80 %), et élimination des clones auto-réactifs $CD19^{+}$/$BCMA^{+}$; bonne tolérance globale

Feng J, et al. Nat Med 2025 Nov;31(11):3725-3736

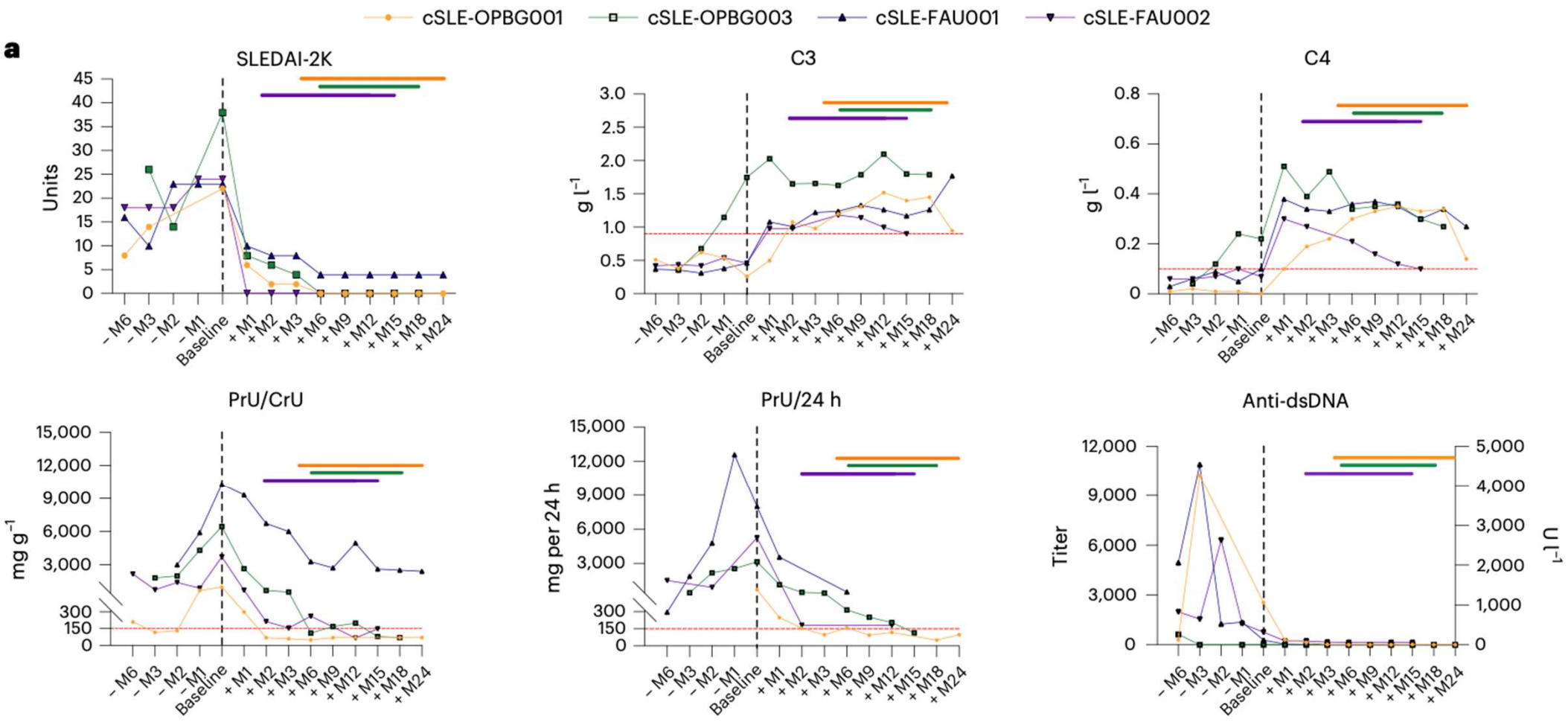
- **CAR-T CD19 allogéniques** : Essai de phase 1 chez 5 LES sévère avec NL. Réponse SRI-4 à M3 chez 5/5 patients puis une poussée légère à M6. Biopsies rénales = résolution de l'inflammation ; bonne tolérance globale

Wang X, et al. Nat Med 2025 Nov;31(11):3713-3724

- **CAR-NK CD19 allogéniques** : Essai de phase 1 incluant 18 patients atteints de LES. Parmi les 9 patients avec suivi ≥ 12 mois, 6 (67 %) ont atteint une rémission ou LLDAS ; bonne tolérance

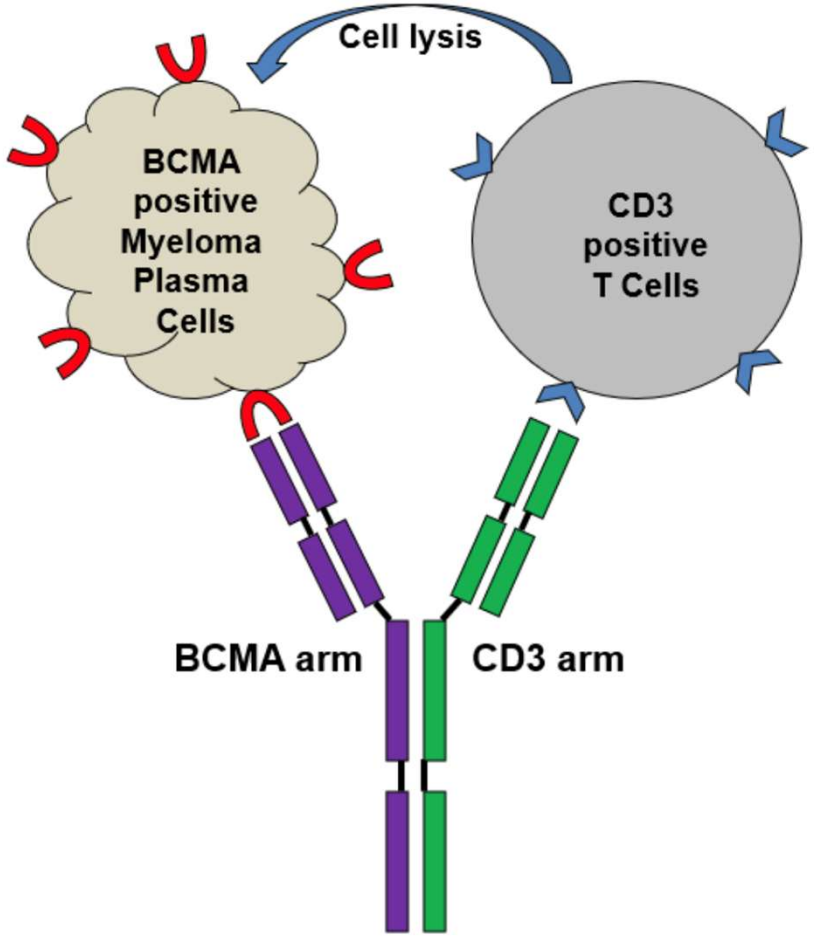
Gao J, et al. Lancet 2026;406(10522):2968-2979

CAR-T en pédiatrie, pour les formes juvéniles agressives



Becilli J, et al. Nat Med 2026

Les bispécifiques dans le lupus systémique



TECLISTAMAB : bispecific T cell engager antibody

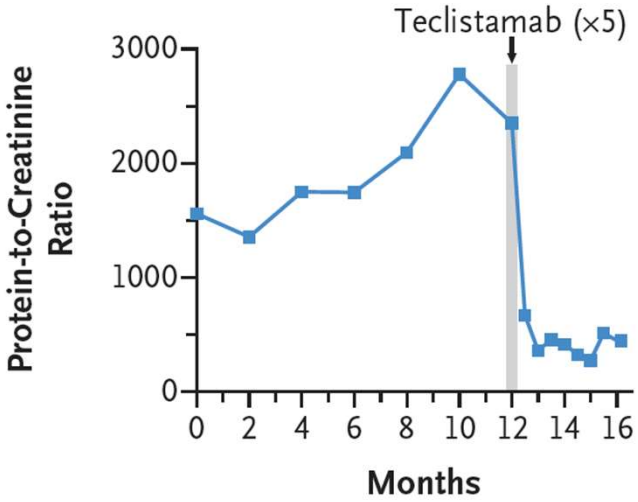
Les bispécifiques dans le lupus systémique

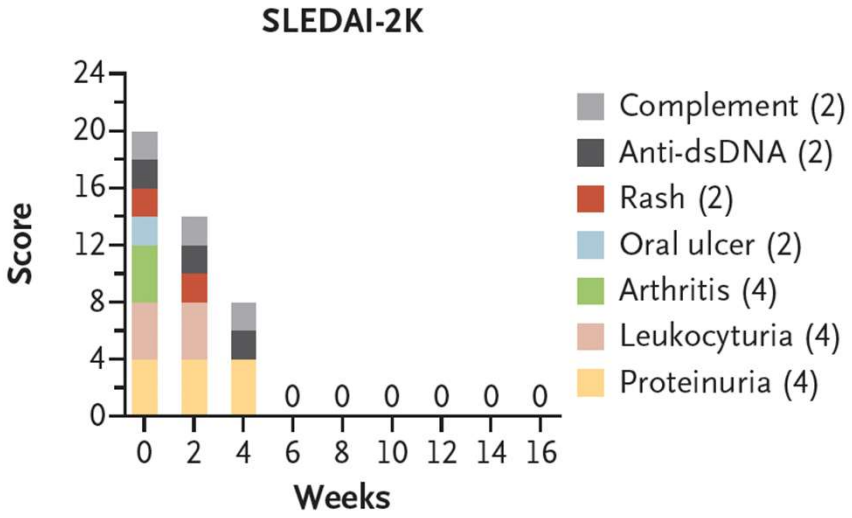
1 patient Lupus systémique

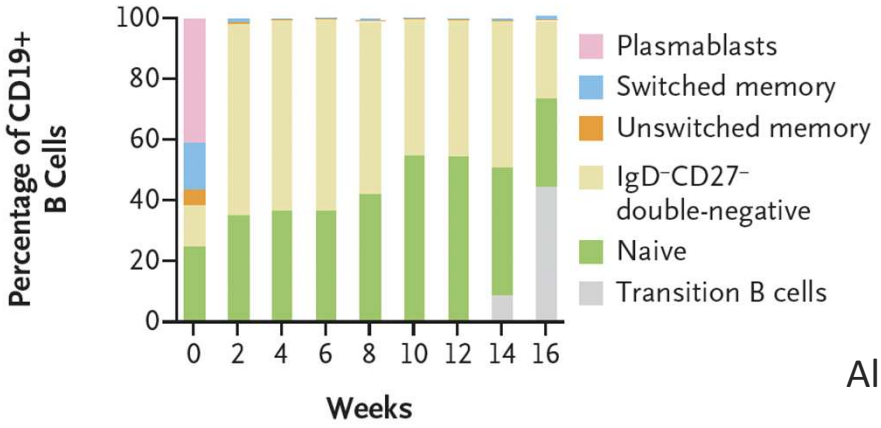
The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Teclistamab-Induced Remission in Refractory Systemic Lupus Erythematosus







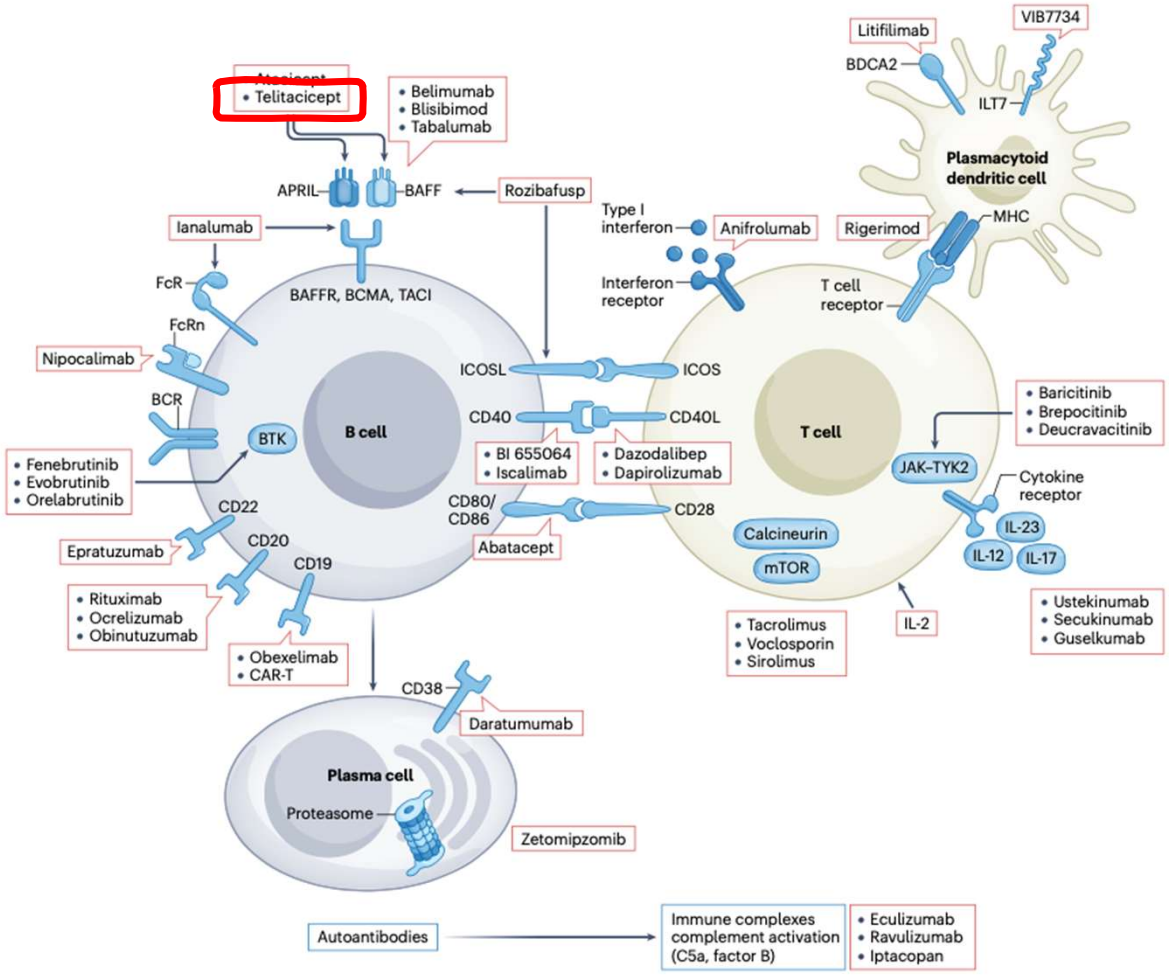
Alexander, NEJM, 2024

CC312, a novel engineered CD19/CD3/CD28 tri-specific antibody leads to rapid and deep B-cell depletion and has broad potential for development in autoimmune diseases

- 5 patients avec lupus réfractaires : 3 à 5μg et 2 à 10 μg
- 0 CRS, 0 ICAN et 0 SAE
- *Rapid and deep depletion of circulating CD19-positive B lymphocytes and their cellular subsets*
- *All five patients achieved SRI-4 response post-intervention, demonstrating significant clinical improvement, including complete symptom resolution in a subset*

Qi J et al. EULAR 2025 ; LB0007

Quels sont les traitements possiblement disponibles à court terme (ou en hors-AMM) ?



Mok CC, et al. Nat Rev Rheumatol. 2023 Mar 2.

Telitacicept dans le lupus systémique

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Telitacicept for Systemic Lupus Erythematosus

Ronald F. van Vollenhoven, M.D.,[1] Li Wang, M.D.,[2] Joan T. Merrill, M.D.,[3] Yi Liu, M.D.,[4] Chunde Bao, M.D.,[5] Fen Li, M.D.,[6] Jiankang Hu, M.M.,[7] Chenghui Huang, M.M.,[8] Jianhong Zhao, M.D.,[9] Cibo Huang, M.M.,[10] Hanyou Mo, M.D.,[11] Wei Wei, M.D.,[12] Fu'ai Lu, M.M.,[13] Jingyang Li, M.D.,[14] Dongbao Zhao, M.D.,[15] Wenxiang Wang, Ph.D.,[16] Lin Li, M.D.,[16] Qing Zuraw, M.D.,[17] Xiaofei Wang, M.D.,[18] Xuebin Wang, M.D.,[18] Jianmin Fang, Ph.D.,[16,20] and Fengchun Zhang, M.D.,[2] for the 18C010 Trial Investigators*

ABSTRACT

BACKGROUND

Telitacicept, a new dual inhibitor of the cytokines B-lymphocyte stimulator (BLyS) and APRIL (a proliferation-inducing ligand), showed efficacy in adults with active systemic lupus erythematosus (SLE) in a phase 2b trial when added to standard therapy.

METHODS

We conducted a phase 3 trial in China in which participants with active SLE were randomly assigned (in a 1:1 ratio) to receive telitacicept (160 mg) or placebo subcutaneously once weekly for 52 weeks, in addition to standard therapy. The primary end point at week 52 was a response on the modified SLE Responder Index 4 (SRI-4), with a response on this composite measure defined as a reduction of at least 4 points in the Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score (ranging from 0 to 105, with higher scores indicating greater disease activity), no new disease activity as measured on the British Isles Lupus Assessment Group index, and no worsening in the Physician's Global Assessment score.

RESULTS

Of 433 adults screened, 335 underwent randomization (167 to the telitacicept group and 168 to the placebo group). At week 52, significantly more participants receiving telitacicept had a response on the modified SRI-4 than those receiving placebo (67.1% vs. 32.7%; adjusted difference, 34.5 percentage points; 95% confidence interval [CI], 24.3 to 44.7; P<0.001). A reduction of at least 4 points from baseline in the SELENA-SLEDAI score had occurred in 70.1% of the telitacicept group and in 40.5% of the placebo group (difference, 29.6 percentage points; 95% CI, 13.1 to 46.1). Adverse events that were considered by the investigator to be related to the trial regimen were more common with telitacicept than with placebo (74.9% vs. 50.0%). Such events that occurred more frequently in the telitacicept group than in the placebo group included upper respiratory tract infection (31.7% vs. 19.0%), a reduced serum IgG level (15.6% vs. 1.2%), a reduced serum IgM level (15.0% vs. 0.6%), and injection-site reactions (12.6% vs. 0.6%).

CONCLUSIONS

In this 52-week trial involving participants with active SLE who were receiving background therapy, the incidence of a clinical response was higher with telitacicept than with placebo. However, the incidence of upper respiratory infections, reduced immunoglobulin levels, and injection-site reactions was also higher with telitacicept. (Funded by RemeGen; 18C010 ClinicalTrials.gov number, NCT04082416.)

Author affiliations are listed at the end of the article. Fengchun Zhang can be contacted at zhangfccra@aliyun.com or at the Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, No. 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China. Ronald F. van Vollenhoven can be contacted at rvanvollenhoven@amsterdamumc.nl or at Amsterdam University Medical Centers, University of Amsterdam, P.O. Box 7057, 1007 MB Amsterdam, the Netherlands. Jianmin Fang can be contacted at jfang@tongji.edu.cn or at the School of Life Science and Technology, Tongji University, 1239 Siping Rd., Shanghai 200092, China.

*A full list of the 18C010 Trial investigators is provided in Supplementary Appendix 2, available at NEJM.org.

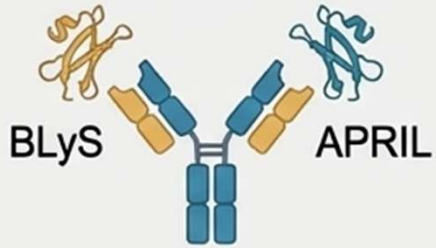
Ronald F. van Vollenhoven and Li Wang contributed equally to this article.

N Engl J Med 2025;393:1475-85.
DOI: 10.1056/NEJMoa2414719

NEJM 2025;393(15):1475-1485

Telitacicept dans le lupus systémique

Design & Population



Essai de phase 3.
Protéine de fusion (TACI-IgG) ciblant conjointement BLyS et APRIL vs Placebo sur 52 semaines.

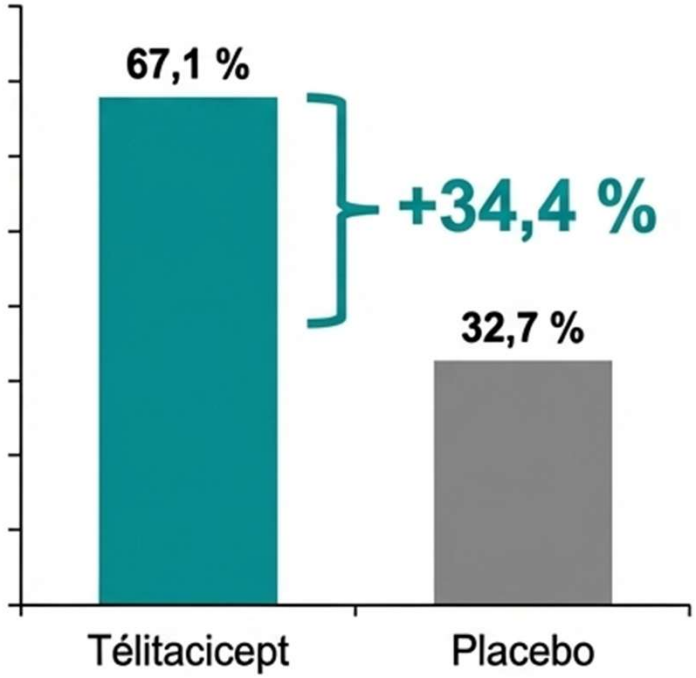
N = 335 patients
(167 Teli, 168 Pbo).

Âge moyen : 34,9 ans.

SLEDAI de base très actif : 11,5.

Différentiel d'Efficacité Massif

Réponse SRI-4 modifiée à S52



Tolérance

Profil de tolérance favorable.

Aucun événement indésirable grave lié au régime de l'essai dans le groupe placebo ou comparatif.

Conclusion

L'inhibition combinée de la maturation des cellules B et de la formation des plasmocytes offre des taux de réponse clinique exceptionnellement élevés par rapport aux standards historiques.

NEJM 2025;393(15):1475-1485

Le B, mais pas seulement : cibler la voie CD40-CD40L

Intérêt de cibler le

:o-immunes

- Rôle central dans les m stimulation
- Expression du CD40 : B cellules épithéliales, er fibroblastes et plaquet
- Expression du CD40L : plaquettes, cellules épi endothéliales
- Production de sCD40L
- Rôle suggéré dans phys Sjögren, PR et sclérode

Thromboembolic complications after treatment with monoclonal antibody against CD40 ligand

To the editor—Exciting results reporting that blockade of the CD40/CD40 ligand pathway by monoclonal antibody against CD40 ligand led to long-term acceptance of renal allografts in monkeys were recently reported in *Nature Medicine*[1] and elsewhere[2]. Our own group has previously reported that mixed chimerism and renal allograft tolerance are achieved in monkeys conditioned with a multi-modality peritransplant regimen and without long-term maintenance immunosuppression[3,4]. In an effort to simplify this therapeutic regimen, we tested a monoclonal antibody against CD40 ligand (American Type Culture Collection catalog number 5C8.33) in this protocol. In the first animals treated, we encountered an unusually high incidence of thromboembolic complications, which we thought worthy of reporting.

Using our standard regimen (nonmyeloablative total body irradiation, thymic irradiation, anti-thymocyte globulin, donor bone marrow infusion and a 1-month course of cyclosporine), we found no thromboembolic complications in more than 50 animals. In contrast, after adding 20 mg/kg of monoclonal antibody against CD40 ligand to the regimen on days 0 and 2, we observed four thromboembolic complications in nine recipients. These included two renal artery thromboses, one renal vein thrombosis and one superior mesenteric artery thrombosis. In subsequent animals, the addition of 100 units/kg heparin immediately before the antibody (days 0 and 2) reduced the incidence of thrombotic complications to just two (one renal artery, one renal vein) in ten recipients. We then tried additional heparin treatments (100 units/kg, days 0,1,2,3) preceded by vigorous postoperative hydration. None of the five animals tested after this change have developed thrombotic complications. These observations may be relevant to ongoing clinical trials of monoclonal antibody against CD40 ligand (humanized version of 5C8) in which some thromboembolic complications have been reported (Vincent, J. *Biogen News* www.prnewswire.com, 11/2/99).

CD40 ligand was originally identified on activated CD4+ T cells[5], later on stimulated mast cells and basophils[6] and most recently on activated platelets *in vitro* and *in vivo* on platelets in the process of thrombus formation[7]. CD40 is constitutively expressed on the vascular endothelium of various organs, and its ligation can upregulate adhesion molecules such as E-selectin, VCAM-1 and ICAM-1. Ligation through CD40 has also been reported to upregulate tissue factor expression on endothelial cells[8]. CD40 ligand expression has also been seen *in vivo* on activated platelets by examining fresh thrombi formed during vessel injury. In all fresh thrombi analyzed, CD40 ligand was expressed on a large proportion of platelets in areas in which densely packed platelets had not yet formed an amorphous mass and on platelets directly adhering to the vessel endothelium. These results may be relevant to the mechanism of a possible increased risk factor for thromboembolism induced by monoclonal antibody against CD40 ligand. Our results indicate that the administration of heparin in conjunction with monoclonal antibody against CD40 ligand can reduce the incidence of thromboembolic complications.

TATSUO KAWAI, DAVID ANDREWS, ROBERT B. COLVIN, DAVID H. SACHS & A. BENEDICT COSIMI
Departments of Surgery and Pathology
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts, USA

Kirk and Harlan reply—Kawai and colleagues report a considerable number of thromboembolic events in monkeys after administration of a mouse monoclonal antibody against human CD154. This group's extensive experience with the monkey kidney allograft model, coupled with their unprecedented run of thrombotic complications, does suggest that something is awry, perhaps that the antibody preparation used in their experiments is prothrombotic. Indeed, a link between CD154:CD40 and coagulation makes great teleological sense. Nevertheless, what makes sense and what is fact are often very different. However appealing, given the reported presence of CD154 on platelets and endothelia, we believe it premature to definitively conclude that the results discussed in this letter are epitope-specific.

Thromboembolic complications have been found after the initial use of many antibodies in humans and monkeys, and have largely disappeared with the use of refined antibody purification processes. Biogen's early clinical trials have been marred by thromboembolic events, indicating that humanized antibody against human CD154 induces thrombosis. These complications have been publicly disclosed and the trials have been halted pending additional pre-clinical evaluation. However, trials (admittedly different in design) using an antibody against human CD154 produced by IDEC Pharmaceuticals have proceeded so far without reported thromboembolic events.

Agents interfering with the CD154:CD40 pathway obviously powerfully influence the immune system and will no doubt have collateral effects. Potential effects, such as the ones presented here, must be scrutinized methodically and then corroborated by rigorous prospective investigation. Only then can important clues derived from anecdotes be accepted as fact.

ALLAN D. KIRK
DAVID M. HARLAN

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2. Kenyon, N.S. *et al.* Long-term survival and function of intrahepatic islet allografts in rhesus monkeys treated with humanized anti-CD154. *Proc. Natl. Acad. Sci. USA* **96**, 8132–8137(1999).
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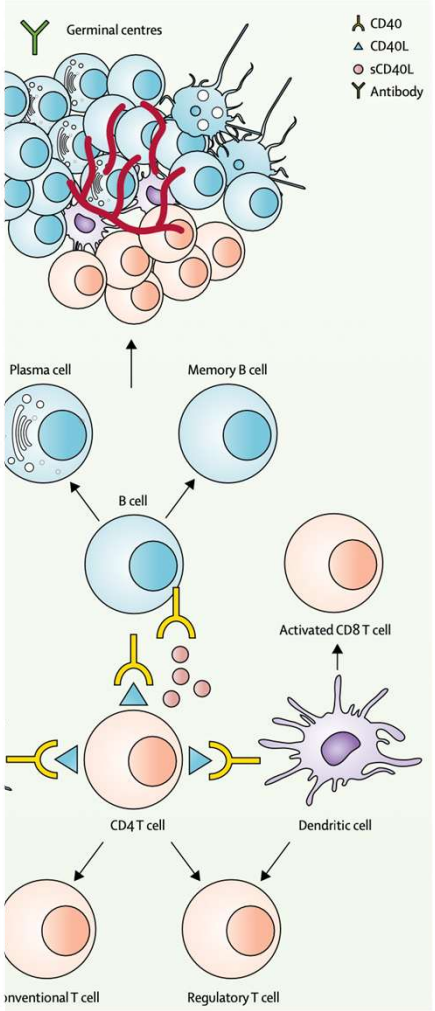

eumatol. 2020 May;2(5):e292-e301

nature medicine

Article

CD40 ligand antagonist dazo
in Sjögren's disease: a rando
double-blinded, placebo-c
phase 2 trial

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Published online: 5 June 2024
Check for updates

E. William St. Clair, Al
Chiara Baldini, Teresa K. T
Valerie Devauchelle-Pen
Tuyet-Hang Pham, Keith

Sjögren's disease (SjD
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A full list of affiliations appears at the end of the pape

Nature Medicine | Volume 30 | June 2024 | 1583

Articles

Safety and efficacy of sub
two distinct populations
(TWINSS): week 24 results
placebo-controlled, phase

Benjamin A Fisher*, Xavier Mariette*, Athena Papas, Thomas G
Ghaith Noaiseh, Sergio Elgueta, Josef Hermann, Sara S McCoy, E
Wen-Lin Luo, Cornelia Scheurer, Wolfgang Hueber, for the TWINS

Lancet 2024; 404: 540–53
Published Online July 31, 2024
https://doi.org/10.1016/S0140-6736(24)01211-X
See Comment page 498
*Joint first authors

Summary

Background Sjögren's disease is a chronic autoimmu
of the TWINSS study is to evaluate the safety and
patients with active Sjögren's disease.

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Funding No

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Department of Rheumatology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK (Prof B A Fisher MD); Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK (Prof B A Fisher); NIHR Birmingham Biomedical Research Centre, Birmingham, UK (Prof B A Fisher); Department of Rheumatology, Université Paris-Saclay, Assistance Publique – Hôpitaux de Paris, Hôpital Bicêtre, INSERM UMR1184, Le Kremlin Bicêtre, France (Prof X Mariette MD PhD); Division of Oral Medicine, Tufts School of Dental Medicine, Boston, MA, USA (Prof A Papas PhD); Division of Rheumatology, Johns Hopkins School of Medicine, Baltimore, MD, USA (T Grader-Beck MD, Prof E Akpek MD); Department of Rheumatology and Clinical Immunology, University of Groningen, University Medical Centre Groningen, Groningen, Netherlands (Prof H Bootsma MD); NIHR Newcastle Clinical Research Facility, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK (Prof W-F Ng PhD); Department of Internal Medicine, Erasmus MC, Rotterdam, Netherlands (P L A van Daele MD); Department of Rheumatology and Clinical Immunology, University Medical Center Freiburg, Faculty of Medicine, University of Freiburg,

540

Eric Jenkins[1], Ingrid Louw[2], Attila Balog[3], Elsa Van Duuren[4], Diane Horowitz[5], Janusz Jaworski[6], Alan Kivitz[7], Ilona Ujfalussy[8], Joe Pirrello[1], Eben Tessari[1], Sheldon Wang[1], John F Paolini[1], on behalf of KPL-404-C211 Investigators

[1]Kiniksa Pharmaceuticals, Lexington, Massachusetts, USA;[2]Panorama Medical Centre, Cape Town, South Africa; [3]Department of Rheumatology and Immunology, Albert Szent-Györgyi Medical School, University of Szeged, 6725 Szeged, Hungary;

Presentation number: L16

Dapirolizumab Pegol Demonstrated Significant Improvement in Systemic Lupus Erythematosus Disease Activity: Efficacy and Safety Results of a Phase 3 Trial

Megan E. B. Clowse,[1] David A. Isenberg,[2] Joan T. Merrill,[3] Thomas Dörner,[4] Michelle Petri,[5] Edward Vital,[6,7] Eric F. Morand,[8] Teri Jimenez,[9] Stephen Brookes,[10] Janine Gaiha-Rohrbach,[11] Christophe Martin,[12] Annette Nelde,[13] Christian Stach[14]

[1]Division of Rheumatology and Immunology, Duke University, Durham, NC, USA; [2]Department of Ageing, Rheumatology and Regenerative Medicine, Division of Medicine, University College London, London, UK; [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, USA; [4]Department of Medicine/Rheumatology and Clinical Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany; [5]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [6]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK; [7]NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [8]Centre for Inflammatory Diseases, Monash University, Melbourne, Australia; [9]UCB, Raleigh, NC, USA; [10]Biogen, Maidenhead, UK; [11]Biogen, Cambridge, MA, USA; [12]UCB, Slough, UK; [13]Biogen, Baar, Switzerland; [14]UCB, Monheim am Rhein, Germany

To receive a copy of this presentation, scan the QR code or visit: UCBposters.com/ACR2024

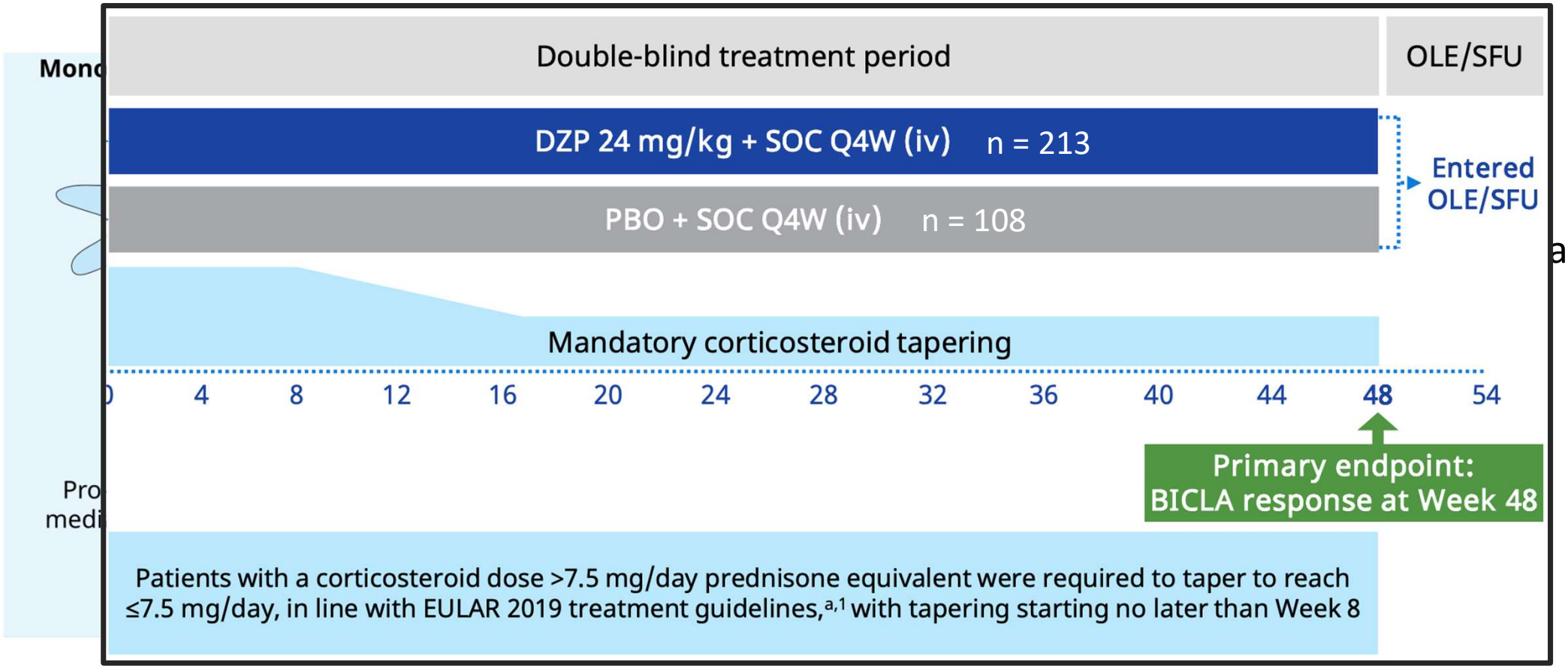
Presentation ID: L16

Link expiration: February 17, 2025

Presented at ACR Convergence 2024 | November 14–19 | Washington, DC

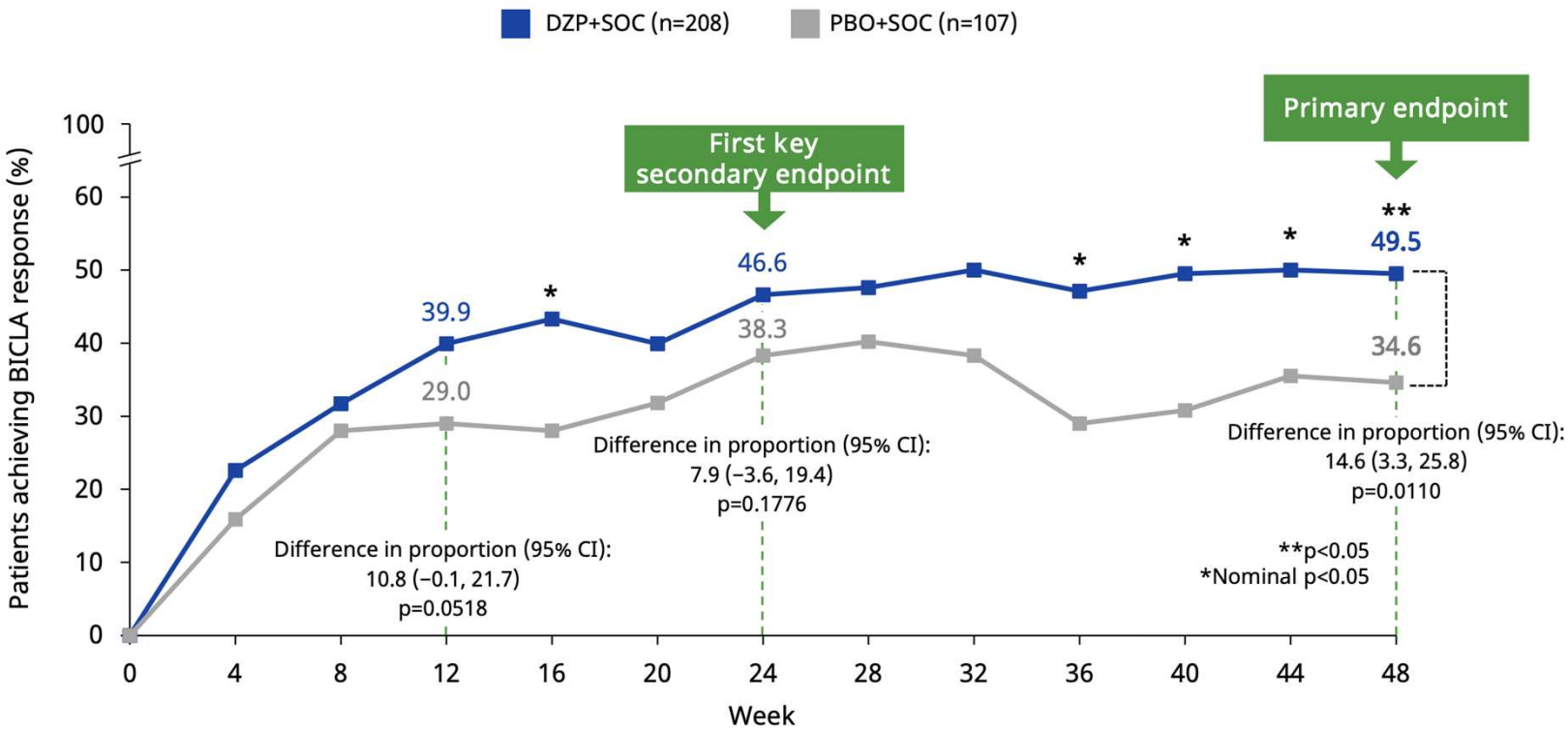
PHOENYCS GO

Dapirolizumab dans le lupus systémique : PHOENYCS GO (1)



Clowse et al, ACR 2024; L16

Dapirolizumab dans le lupus systémique : PHOENYCS GO (2)

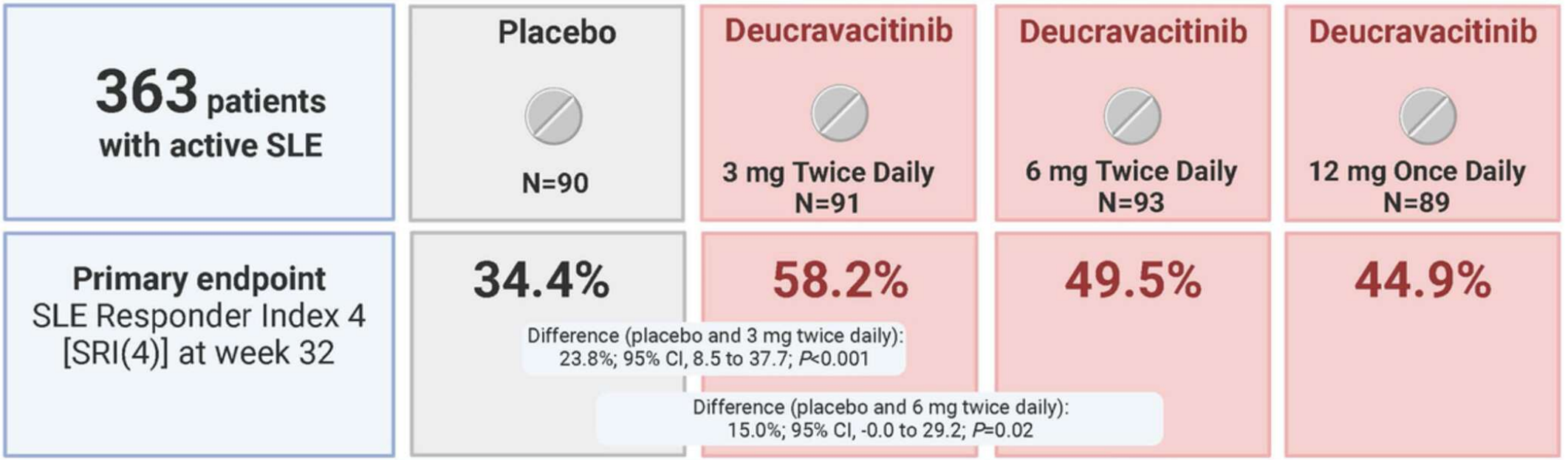


- Tolérance
  - effets secondaires sévères 9,9% avec DZP et 14,8% avec PBO
  - 1 IDM avec DZP et 1 décès

Clowse et al, ACR 2024; L16

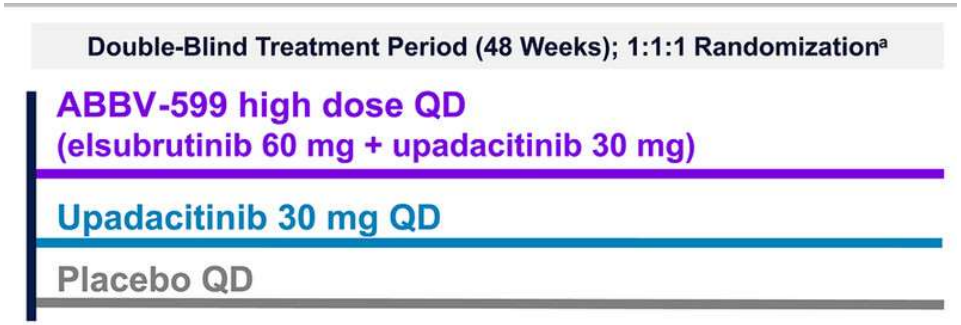
Et les JAKis ?

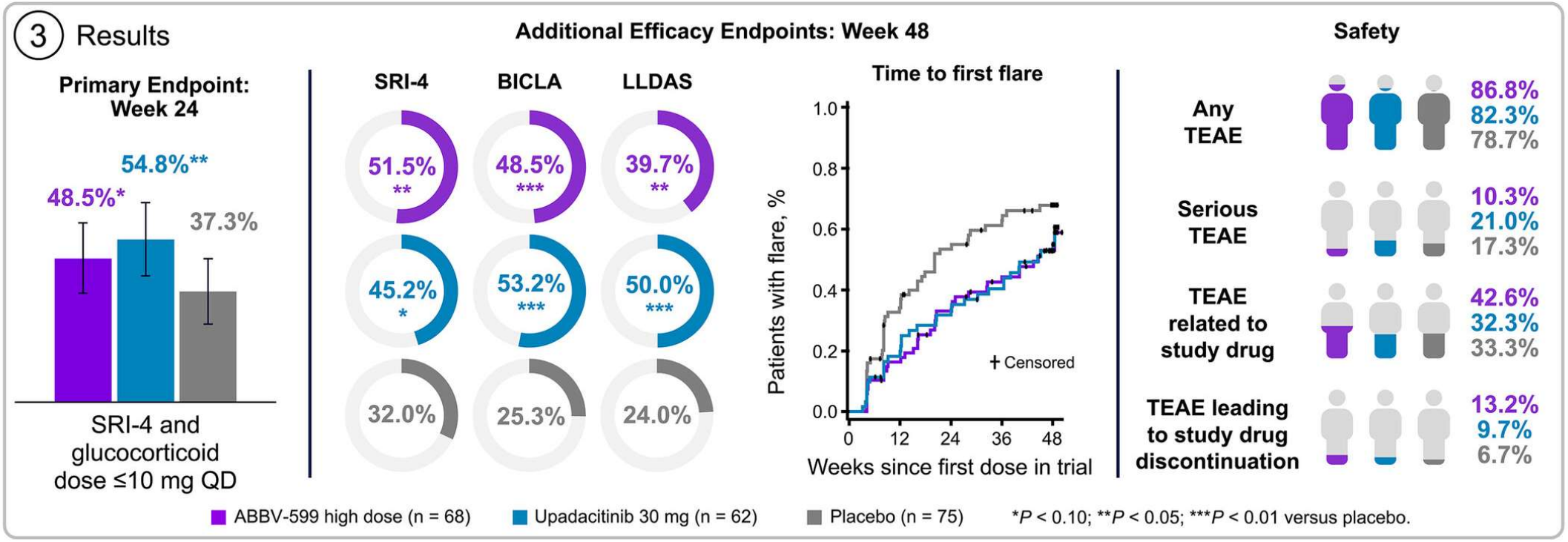
Deucravacitinib



Morand E, Arthritis Rheumatol, 2022

Upadacitinib





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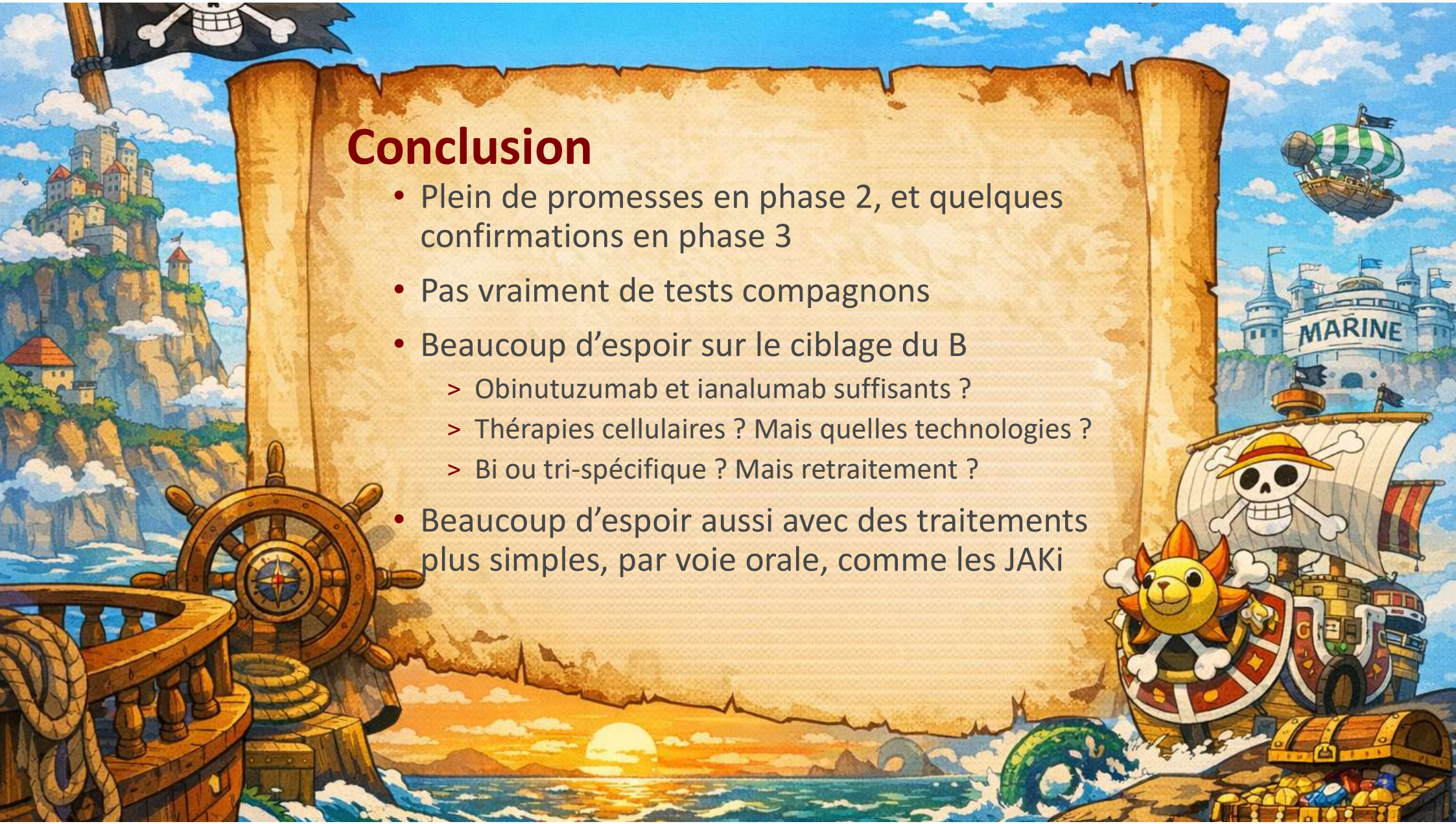

Conclusion

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- Pas vraiment de tests compagnons
- Beaucoup d'espoir sur le ciblage du B
  - > Obinutuzumab et ianalumab suffisants ?
  - > Thérapies cellulaires ? Mais quelles technologies ?
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