These handouts are designed to complement the expert presentations. We strongly encourage you to view the full sessions before drawing conclusions based solely on the handout content.

This information is current at the time of recording and is subject to change as new information becomes available.

Therapies on the Horizon - I

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Disclosures

- Consulting/Advisory Board:

Novartis, Janssen, Amgen, Argenx.

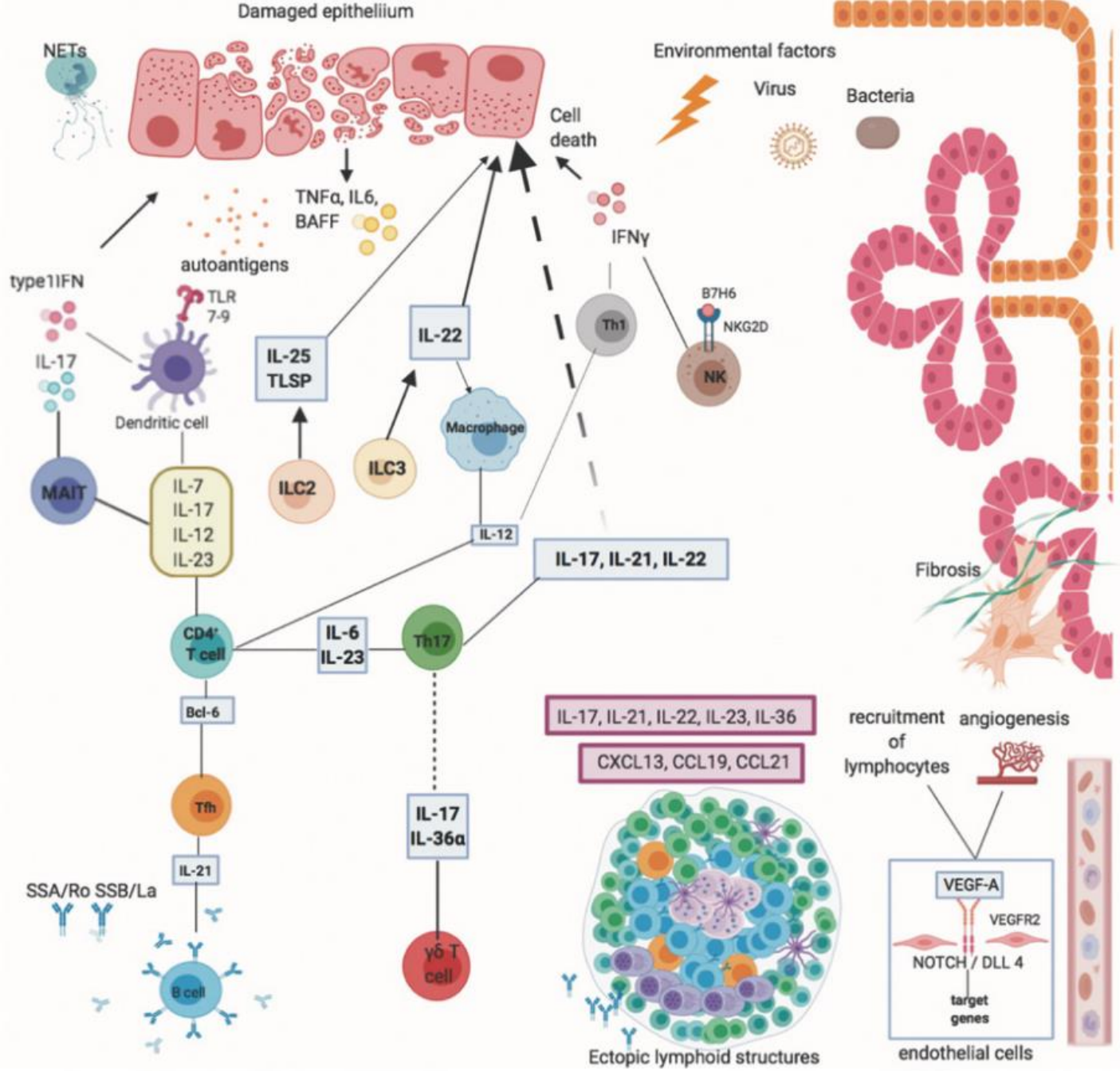
- Clinical trials support:

Novartis, Janssen, Amgen, BMS, Pfizer, Sanofi, Horizon.

Presentation Outline

1. Review - Immune system changes in Sjogren's
2. Deucravacitinib
3. Dazodalibep
4. Ianalumab

Pathophysiology of Sjogren's Disease



Fasano S, Mauro D, Macaluso F, et al. *Pathogenesis of primary Sjögren's syndrome beyond B lymphocytes.* Clin Exp Rheumatol. 2020;38(Suppl 126):S315-S323.

Understanding Sjögren's Disease
A Step-by-Step Guide

1. What Starts It?

- Some people have genes that make them more likely to get SjD

- Things like certain viruses or hormone changes can trigger it

2. What Happens in the Glands?

- Cells in saliva and tear glands start acting like they're fighting germs

- They call in help by sending signals (called cytokines and chemokines)

3. First Responders

- Immune cells like macrophages and dendritic cells arrive

- They release substances that can damage tissues

4. More Immune Cells Join

- T and B cells gather around the glands

- This is a key sign doctors look for

5. B Cells Go Into Overdrive - Special signals help B cells grow and survive. - They make antibodies that can cause problems.

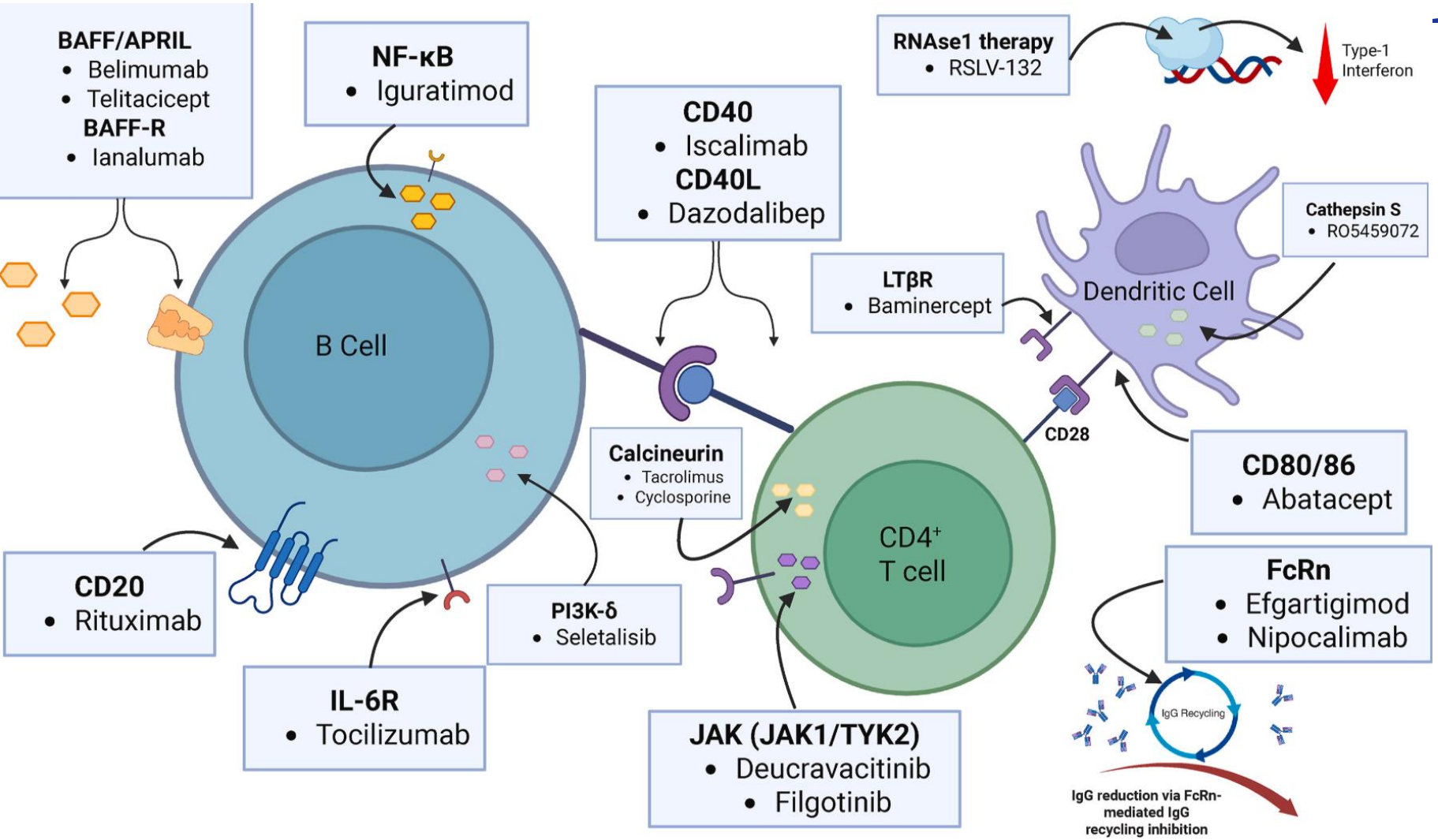
6. Damage from Antibodies - These antibodies form clumps that can hurt tissues. - They may cause inflammation in skin, kidneys, and nerves.

7. Important Substances Involved - Many signals are involved: interferons, interleukins, and BAFF.

8. Long-Term Effects - Dry mouth and eyes are common. - Some people feel tired or have joint pain.

9. Same Process can repeat in other organs such as the lung, or kidney

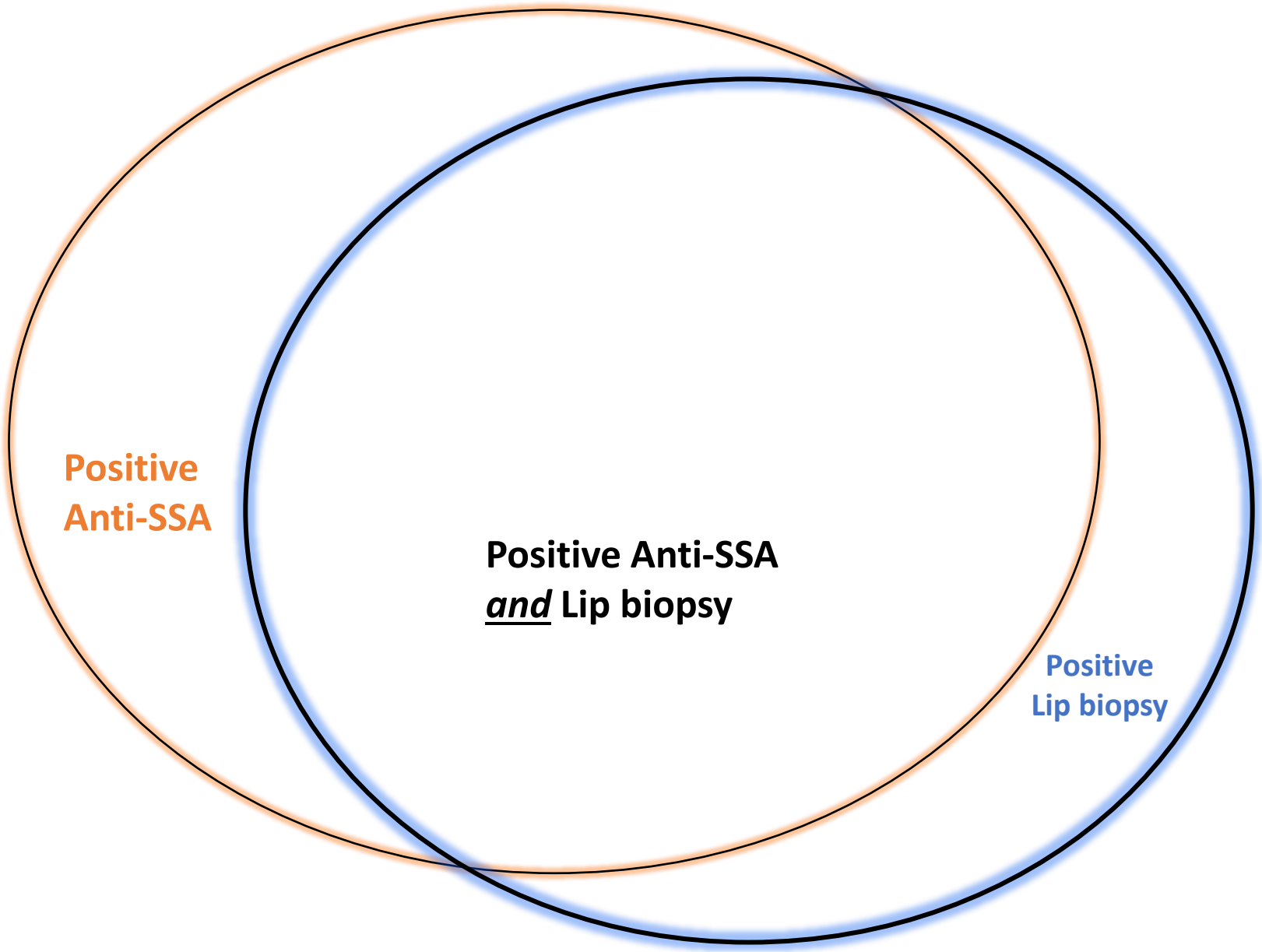
Experimental therapies in SJD



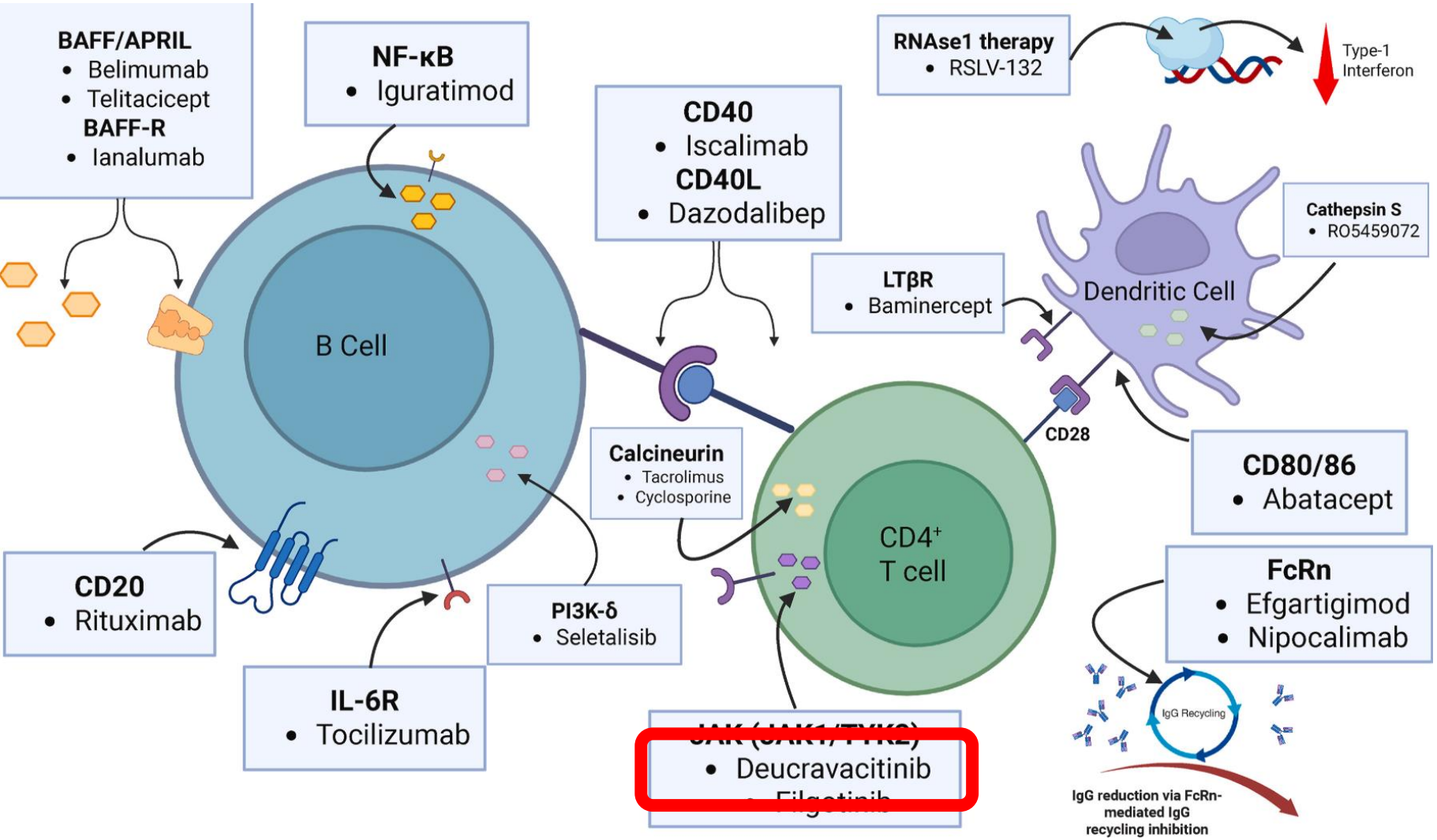
Novel therapies in Sjogren's disease: A systematic review of the literature.Pelkas C, Franke KB, Vincent FB, Rischmueller M.Best Pract Res Clin Rheumatol. 2025 Jul 7:102084

Key points

- We do not Fully understand how the immune system is dysregulated in SJD, but we have a general idea
- New research sheds light on the intricate interaction between inflammatory cells and how this causes organ damage
- Such incomplete understanding is an important reason why some clinical trials fail
- Certain pathway of inflammation may be more important than others and we would not know this



Deucravacitinib



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Post Hoc analysis from Phase II SLE trial

American College of Rheumatology
Empowering Rheumatology Professionals

MEETINGS • KEYWORD INDEX • ADVANCED SEARCH • YOUR FAVORITES • ACR MEETINGS

ABSTRACT NUMBER: 0620

Clinical Efficacy and Patient-Reported Outcomes in Anti-Ro/Sjögren's Syndrome–Related Antigen a Antibody–Positive Patients with Active SLE Treated WithDeucravacitinib in the Phase 2 PAISLEY Trial

Benjamin A. Fisher[1], Hendrika Bootsma[2], Vibeke Strand[3], Wan-Fai Ng[4], Thomas Wegman[5], Brandon Becker[6], Jiyoon Choi[6], Antoine Sreih[6], Leo Chen[7], Antonia Christodoulou[6] and Eric Morand[8], [1]University of Birmingham, Birmingham, United

Deucravacitinib – Post Hoc analysis

Study design

- Lupus study ! (363 pts)
- Looked at subgroup with positive anti SSA
- *Post hoc* analysis performed
- Over 50% of SLE pts were anti-SSA + (188 pts)

- This group improved in terms of SLE and also fatigue & pain

- Jump immediately to P-III Sjogren's study !

Deucravacitinib -Phase 3 Design

Study design

- Oral tablet (3mg, 6 mg) Vs placebo
- PE: Change from baseline in ESSDAI Vs PCBO at week 52

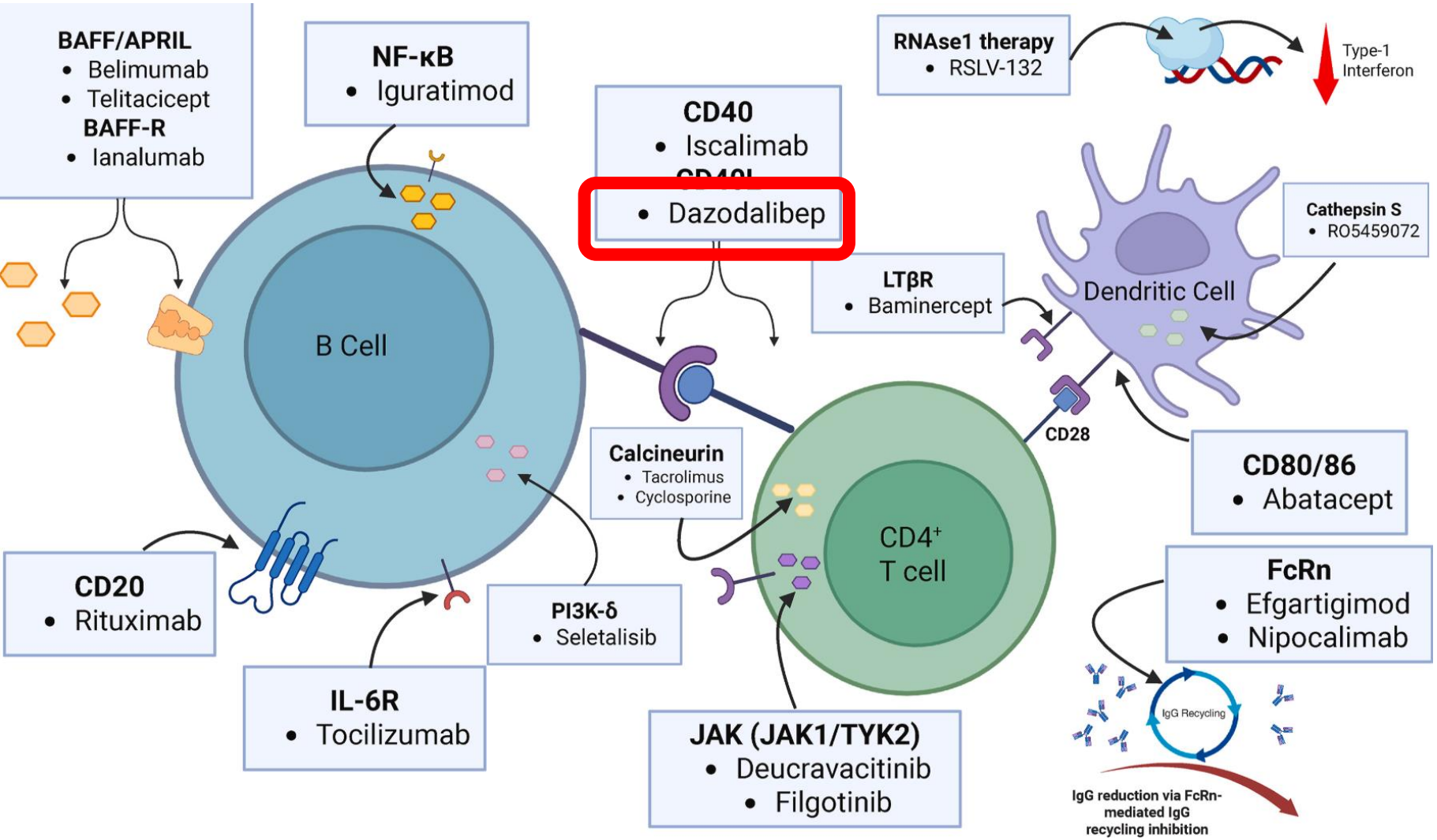
Key inclusion/ Exclusion

- SjD by 2016 criteria (SSA +)
- ESSDAI >= 5
- Positive SSA
- Some residual saliva
- No -Severe complications of SjS (vasculitis, lymphoma, active CNS – renal lung)
- Active infection and/or febrile illness not related to SjS within 14 days

Deucravacitinib who might be suited to it?

- Patients with an **interferon-high**, autoantibody-positive profile are prime candidates
- Anti-SSA antibody positive
- B cell Hyperactivity
- Evidence of B cell Hyperactivity
  - High immunoglobulin G levels – Hypergammaglobulinemia
  - Positive rheumatoid factor
  - Positive cryoglobulins
  - Low complement (C3, C4)

Dazodalibep



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Dazodalibep-Phase 2 Study

nature medicine

Article

https://doi.org/10.1038/s41591-024-03009-3

CD40 ligand antagonist dazodalibep in Sjögren's disease: a randomized, double-blinded, placebo-controlled, phase 2 trial

Received: 21 December 2023

Accepted: 18 April 2024

Published online: 05 June 2024

Check for updates

E. William St. Clair[1], Alan N. Baer[2], Wan-Fai Ng[3,4,5], Ghaith Noaiseh[6], Chiara Baldini[7], Teresa K. Tarrant[1,8], Athena Papas[9], Valerie Devauchelle-Pensec[10], Liangwei Wang[11], Wenjing Xu[11], Tuyet-Hang Pham[11], Keith Sikora[11], William A. Rees[11] & Ilias Alevizos[11]

Dazodalibep-Phase 2 Study

Design

- 1:1 IV 1500 mg Dazodalibep or placebo every 4 weeks
- Primary endpoint:

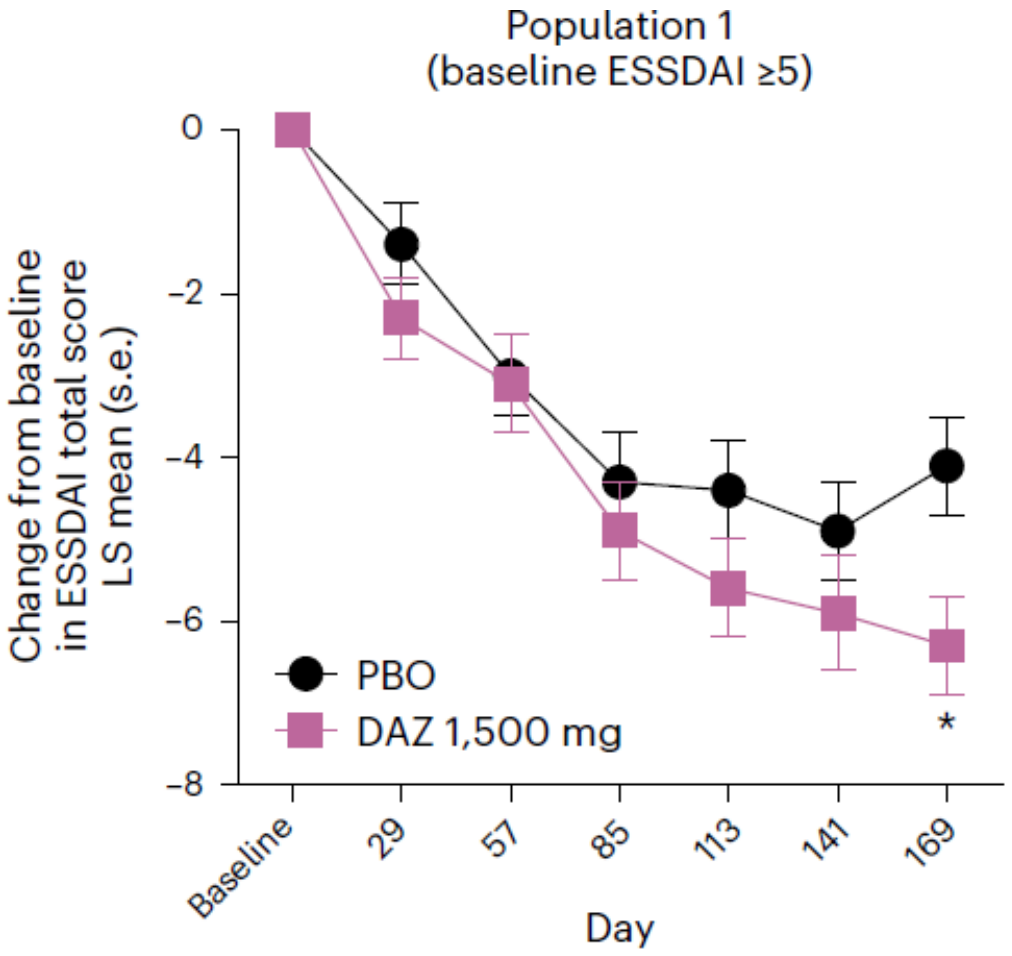
ESSDAI in Population I @ 24 wk

ESSPRI in Population II @ 24 wk

Key inclusion criteria

- 2016 ACR/EULAR criteria
- Anti-Ro/SSA+ or RF+
- ESSDAI ≥5 in P-I
- ESSPRI ≥5 **&** ESSDAI <5 in P-II

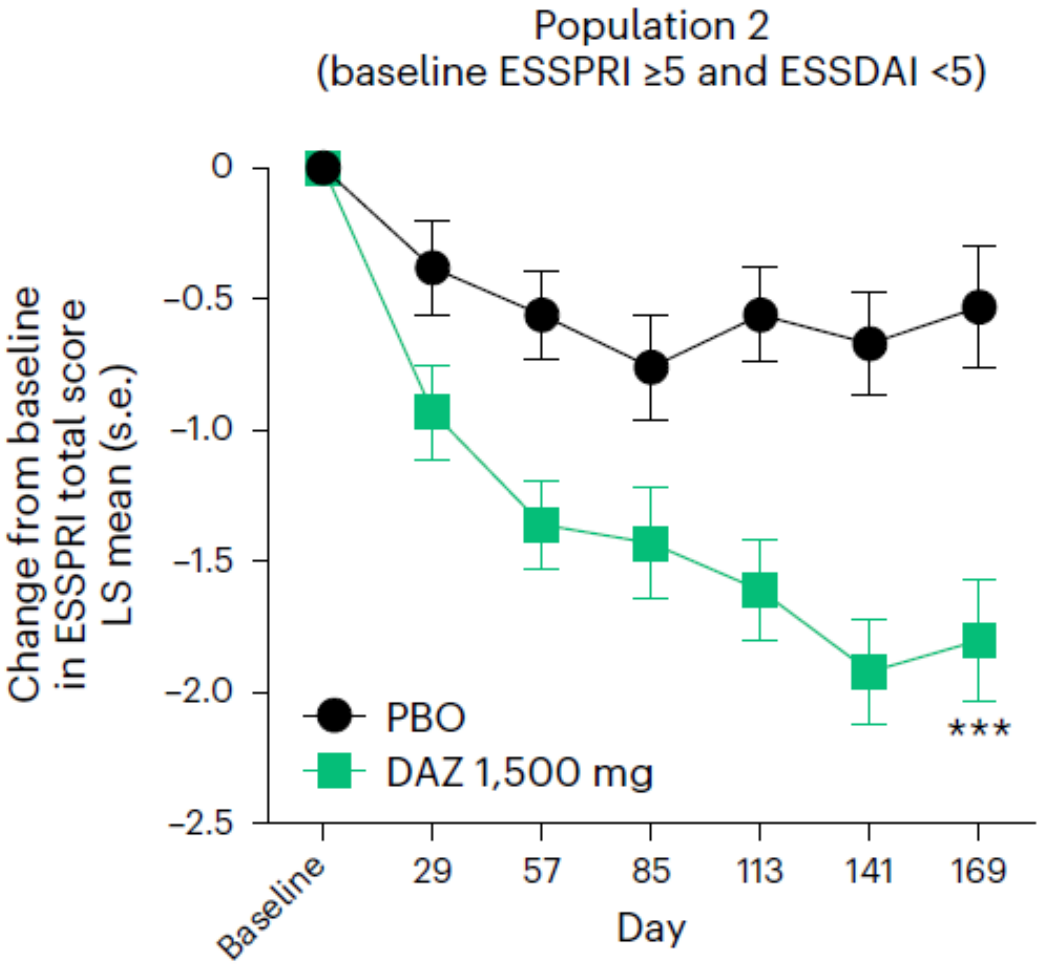
Dazodalibep-Phase 2 – Population I



- 74 pts recruited
- Patients with high systemic activity did better than placebo @ day 169 (6 months)
- - 6.3 improvement in ESSDAI in treatment arm Vs

  - 4.1 in PCBO arm

Dazodalibep-Phase 2 – Population II



- 109 pts recruited
- Patients with high symptoms burden did better than placebo @ day 169 (6 months)
- - 1.8 points (out of 10) improvement in ESSPRI in treatment arm Vs

  - 053 in PCBO arm

Dazodalibep-Phase 3 Design -301 (P-I)

Study design

- IV infusion (1500 mg , 3000 mg) Vs placebo
- PE: Change from baseline in ESSDAI Vs PCBO

Key inclusion/ Exclusion

- SjD by 2016 criteria
- ESSDAI >= 5
- Positive SSA or RF
- No Hx of herpes zoster
- No blood clots last 2 years
- No active infection requiring Abx last 12 months

Dazodalibep-Phase 3 Design -303 (P-II)

Study design

- IV infusion (two doses) Vs placebo
- PE: Change from baseline in ESSPRI Vs PCBO

Key inclusion/ Exclusion

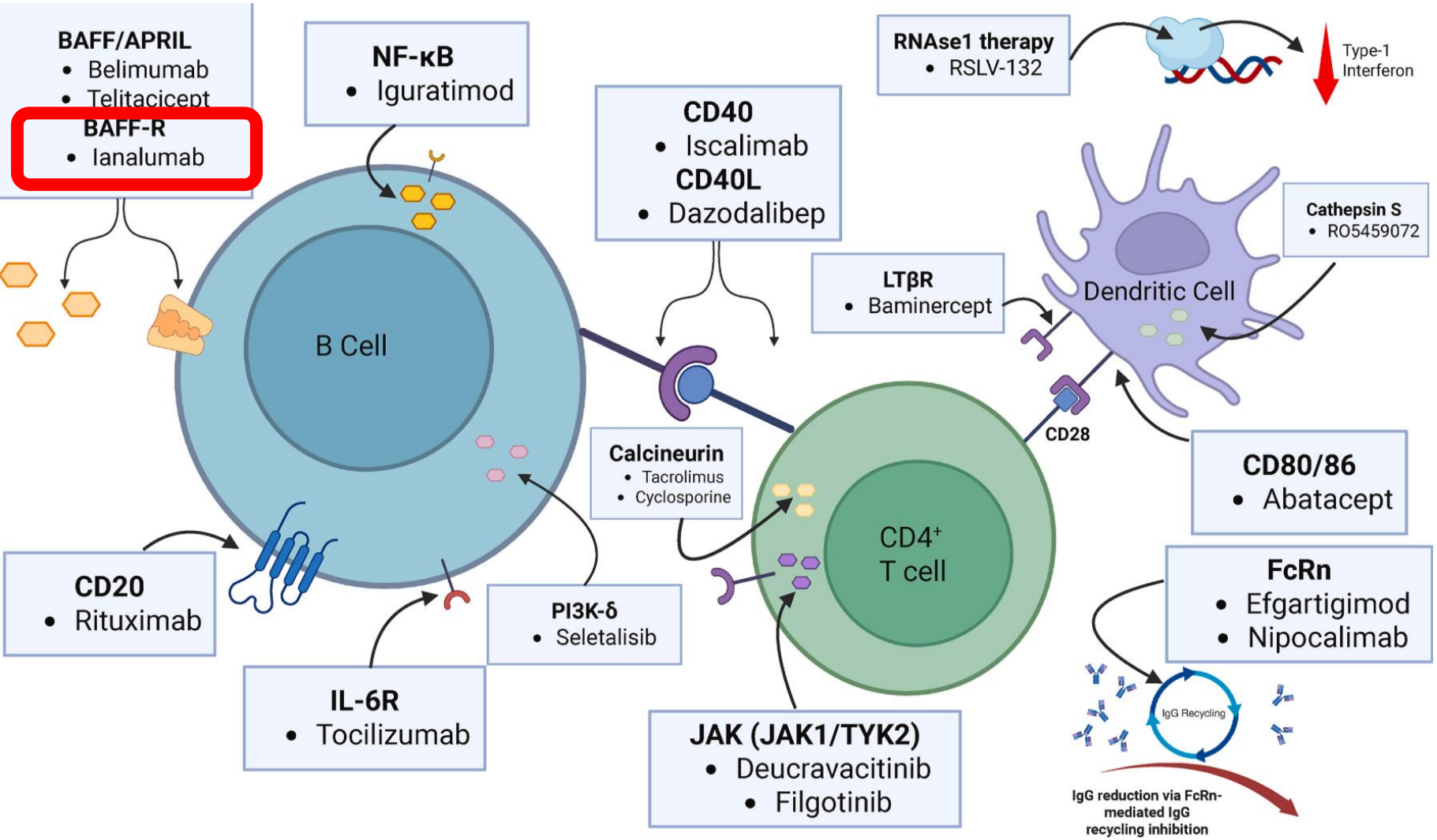
- SjD by 2016 criteria
- ESSPRI >=5
- ESSDAI <5
- Positive SSA or RF
- No Hx of herpes zoster
- No blood clots last 2 years
- No active infection requiring Abx last 12 months

Dazodalibep- who might be suited to it?

- *Unique → Symptom Phenotype* – **Patients with severe sicca symptoms (dry mouth, dry eyes) and/or fatigue** are excellent candidates

- Similar to prior → Anti-SSA antibody positive or RF positive with B cell Hyperactivity

Ianalumab



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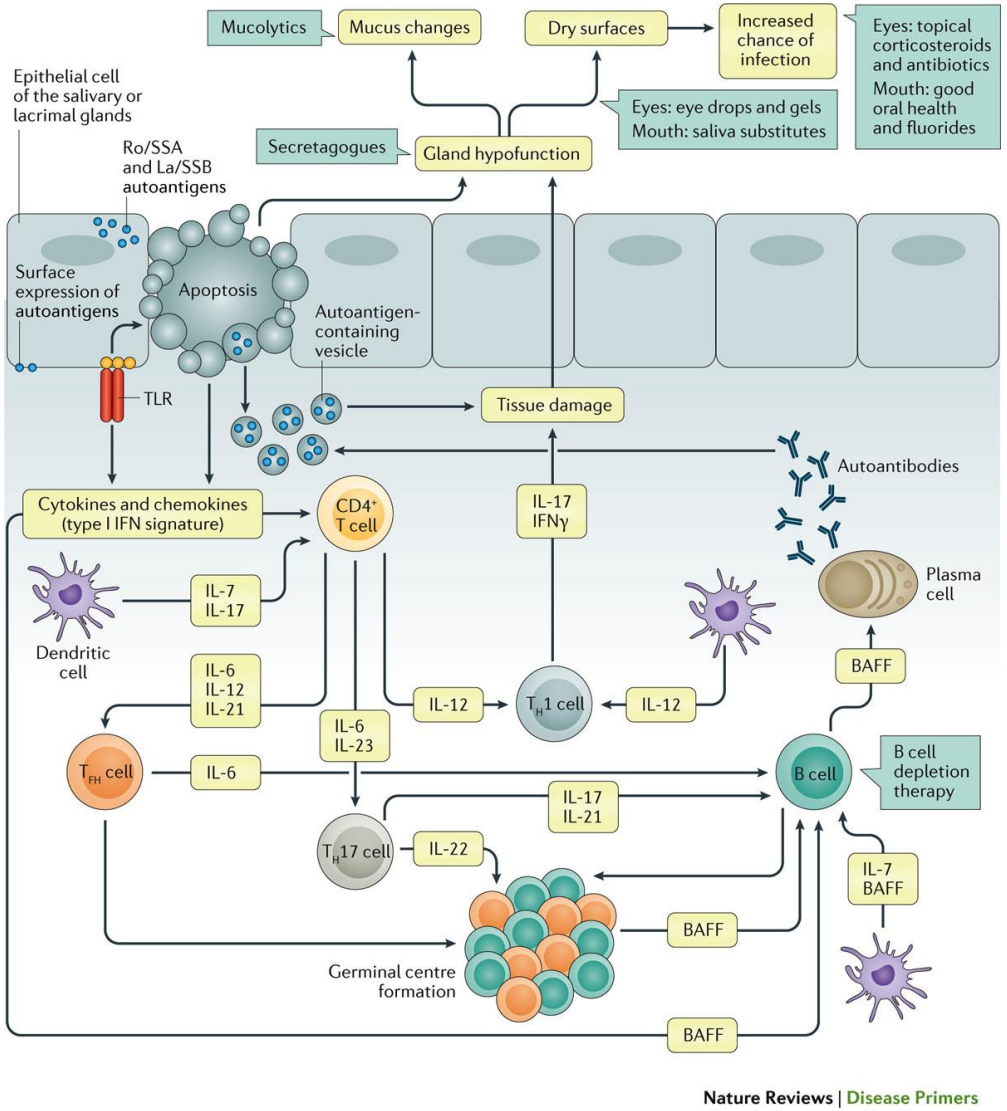
Ianalumab

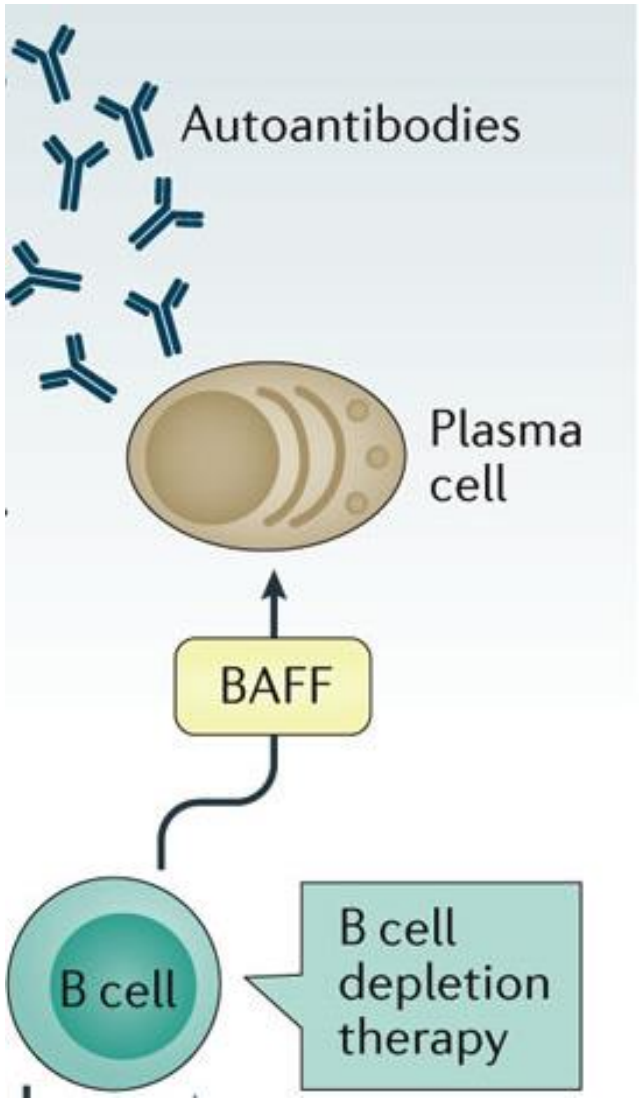
- Monoclonal antibody
- Binds to the receptor for B-cell activating factor (BAFF)

- Direct B-cell depletion
- BAFF:BAFF-R signaling blockade

What does this mean?

- Depletes active B-cells
- Prevents new B cells from maturing and surviving → Apoptosis (programed death)





Brito-Zerón, P. *et al. Nat. Rev. Dis. Primers* (2016)

Ianalumab -Phase 2 Study

Safety and efficacy of subcutaneous ianalumab (VAY736) in patients with primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled, phase 2b dose-finding trial

Simon J Bowman, Robert Fox, Thomas Dörner, Xavier Mariette, Athena Papas, Thomas Grader-Beck, Benjamin A Fisher, Filipe Barcelos, Salvatore De Vita, Hendrik Schulze-Koops, Robert J Moots, Guido Junge, Janice N Woznicki, Monika A Sopala, Wen-Lin Luo, Wolfgang Hueber

Ianalumab - Phase 2 Study

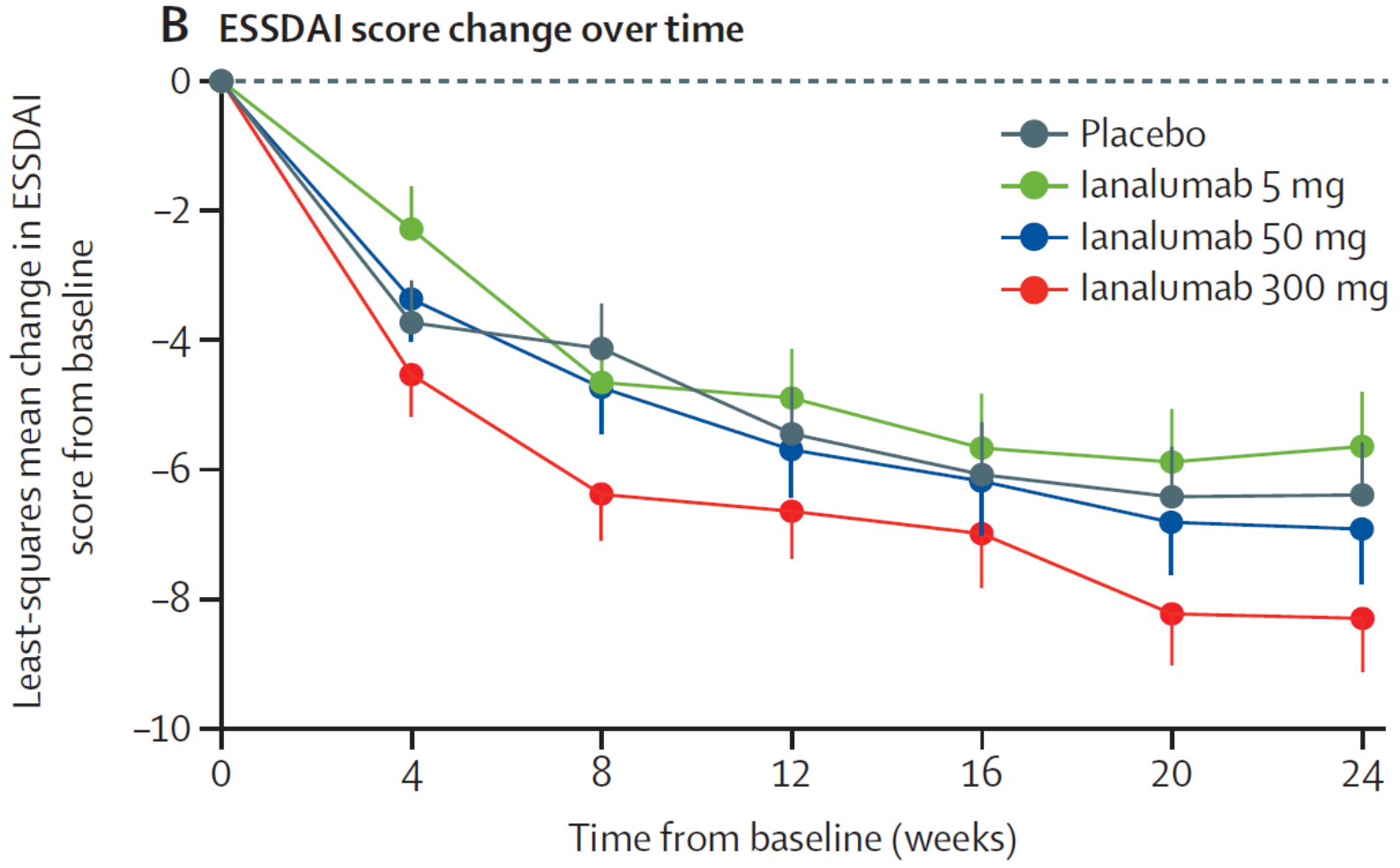
Design

- 1:1:1:1 SC injections Ianalumab (5 mg, 50 mg, or 300 mg) or placebo every 4 weeks (total 190 pts)
- Primary endpoint: ESSDAI change at week 24

Key inclusion/ Exclusion

- SjD by 2016 criteria (SSA+)
- ESSDAI >= 5 **AND** ESSPRI >=5
- Positive SSA
- Some residual saliva
- No recent malignancy
- No active infection

Ianalumab -Phase 2



Ianalumab -Phase 3 Design

Study design

- SC injections **(300mg QM, 300mg Q3M)** Vs placebo

- PE: Change from baseline in ESSDAI Vs PCBO @ week 48

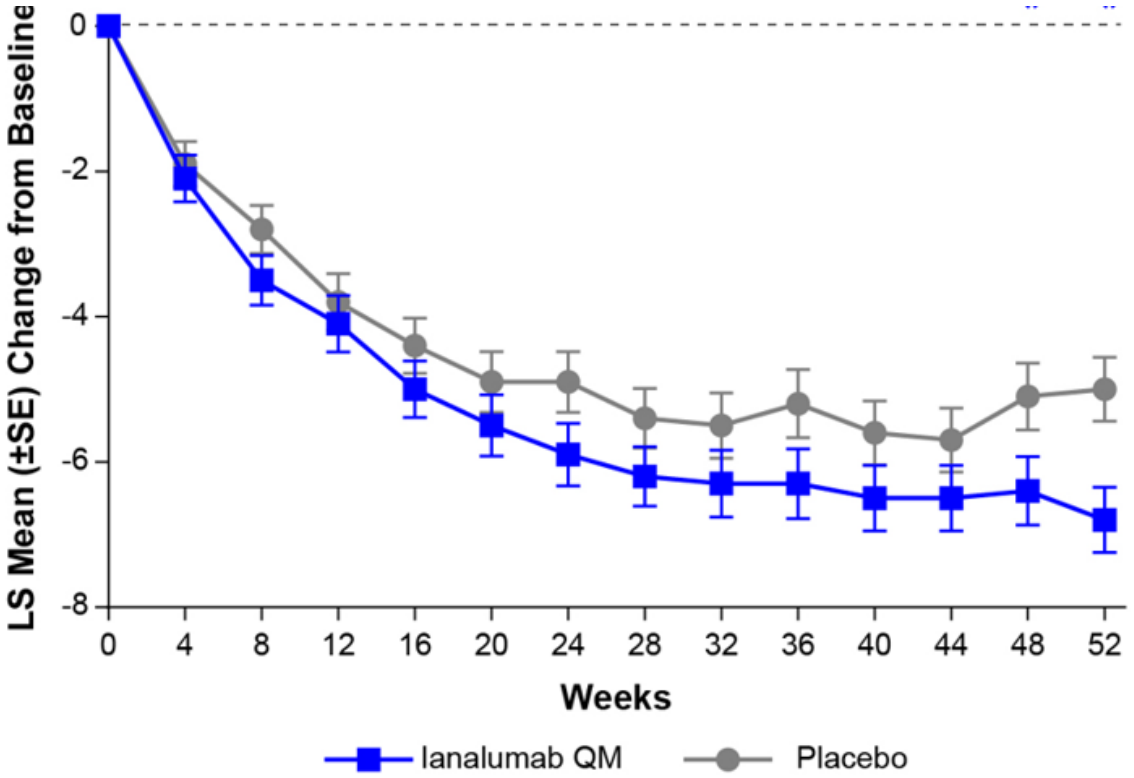
Key inclusion/ Exclusion

- SjD by 2016 criteria
- Time since diagnosis ≤ 7.5 years
- ESSDAI >= 5
- Positive SSA (in 90%) + MSGB in 10%
- Some residual saliva
- No cancer within 5 years
- No active infection

Ianalumab –Neptunes -1 result

- In N1, **275** pts were randomized

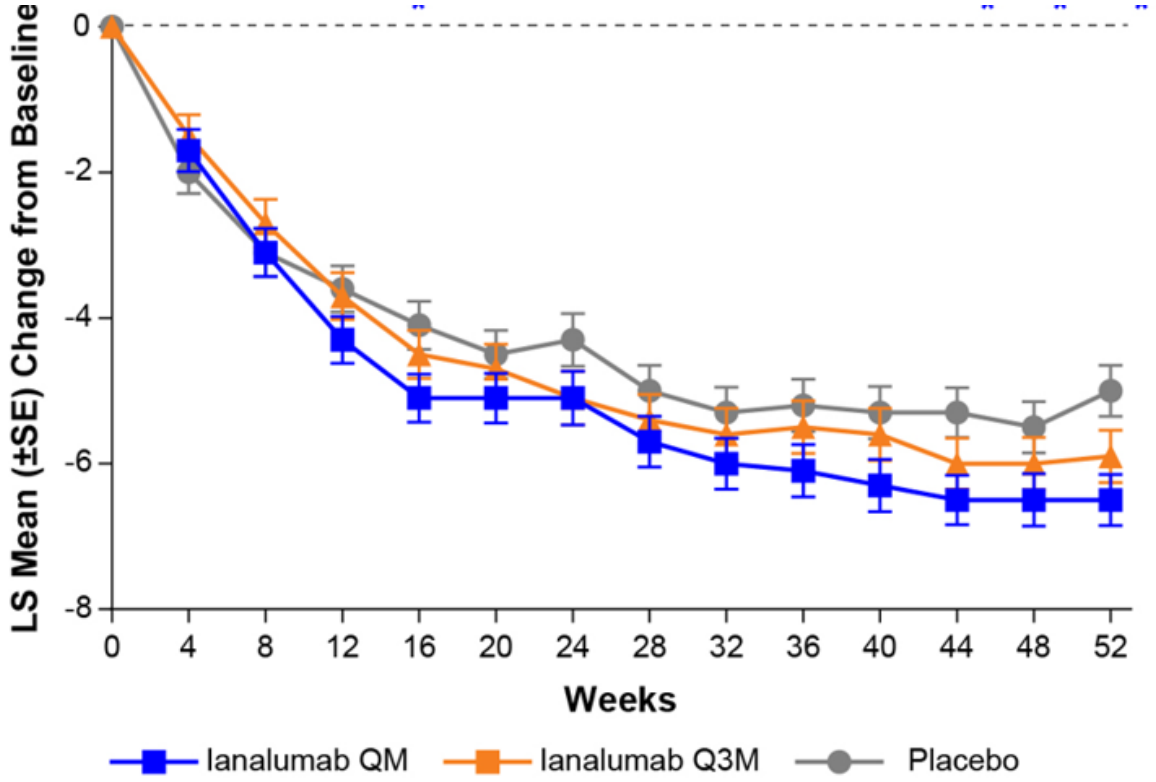
- Primary end point met
- Patient and physician global assessments also improved
- Safety was encouraging



Neptunes - 1

Ianalumab –Neptunes -2 result

- In N2, **504** pts were randomized
- Primary end point met
- Safety was encouraging



Neptunes - 2

Ianalumab - who might be suited to it?

- Similar to prior → Anti-SSA antibody positive or RF positive with **B cell Hyperactivity**

Conclusion

- VERY exciting era for Sjogren's research !
- We will likely have the first FDA approval in 2026
- And, likely, a few more by 2028-2029 !
- This will help synthesize more data to enable better care !

Thank you