Treatment Updates in MS and NMOSD

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Disclosures

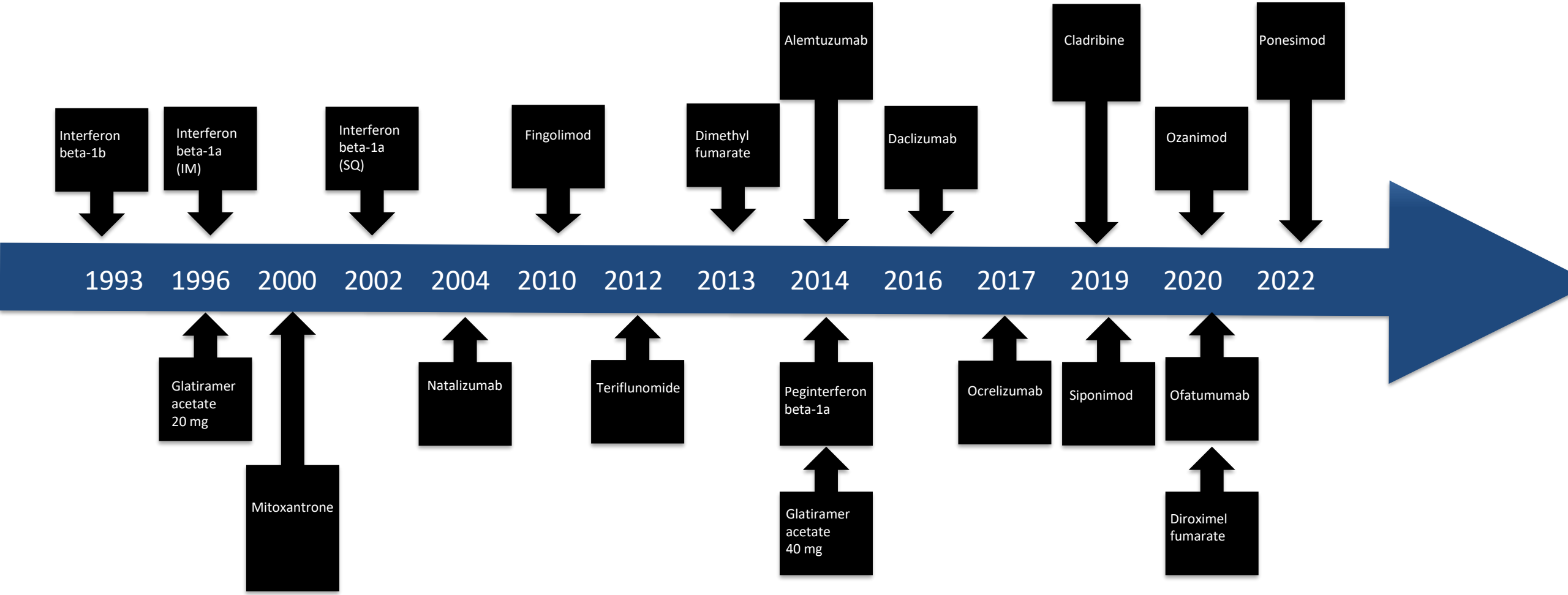
- Unpaid member of the The MOG Project medical advisory board
- Site Principal investigator for clinical trial sponsored by Sanofi
- Site Principal investigator for clinical trial sponsored by Novartis
- Paid work for NeurologyLive

Objectives

- Treatment updates in MS
- MS Treatments on the horizon
- Treatment updates in NMOSD
- NMOSD Treatments on the horizon

Multiple Sclerosis

MS Treatment Landscape



The last 5 years

Ocrelizumab

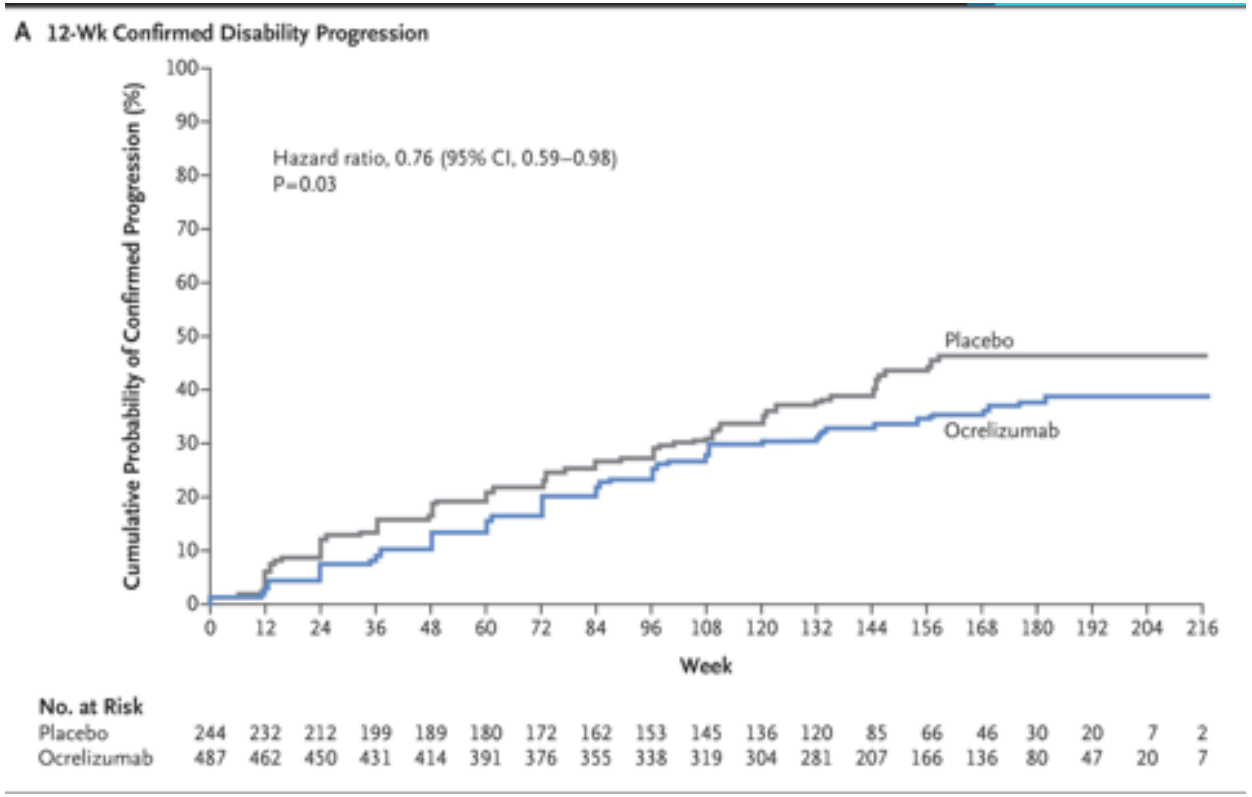
- Approved in March 2017
  - RRMS, active SPMS,PPMS
- MOA: Anti-CD20 monoclonal antibody
- Every 6 month infusion

Ocrelizumab

- Side Effects
  - Infusion related reactions
  - Increased risk of infection
  - Neoplasm
  - PML – 12 cases as of March 2022
- Monitoring
  - Pre-labs - Hep B studies, Hep C, quantiferon gold, CBC and CMP, baseline line immunoglobulin levels
  - Monitoring – yearly TB, Hep B studies. CBC and CMP Q6 months.

ORATORIO (PPMS)

- Ocrelizumab vs placebo
- Primary end-point – percentage of patients with disability progression (EDSS)
  - 12 weeks - 32.9% vs 39.3%
  - 24 weeks – 29.6% vs 35.7%



Montalban X, et al. N Engl J Med. 2017

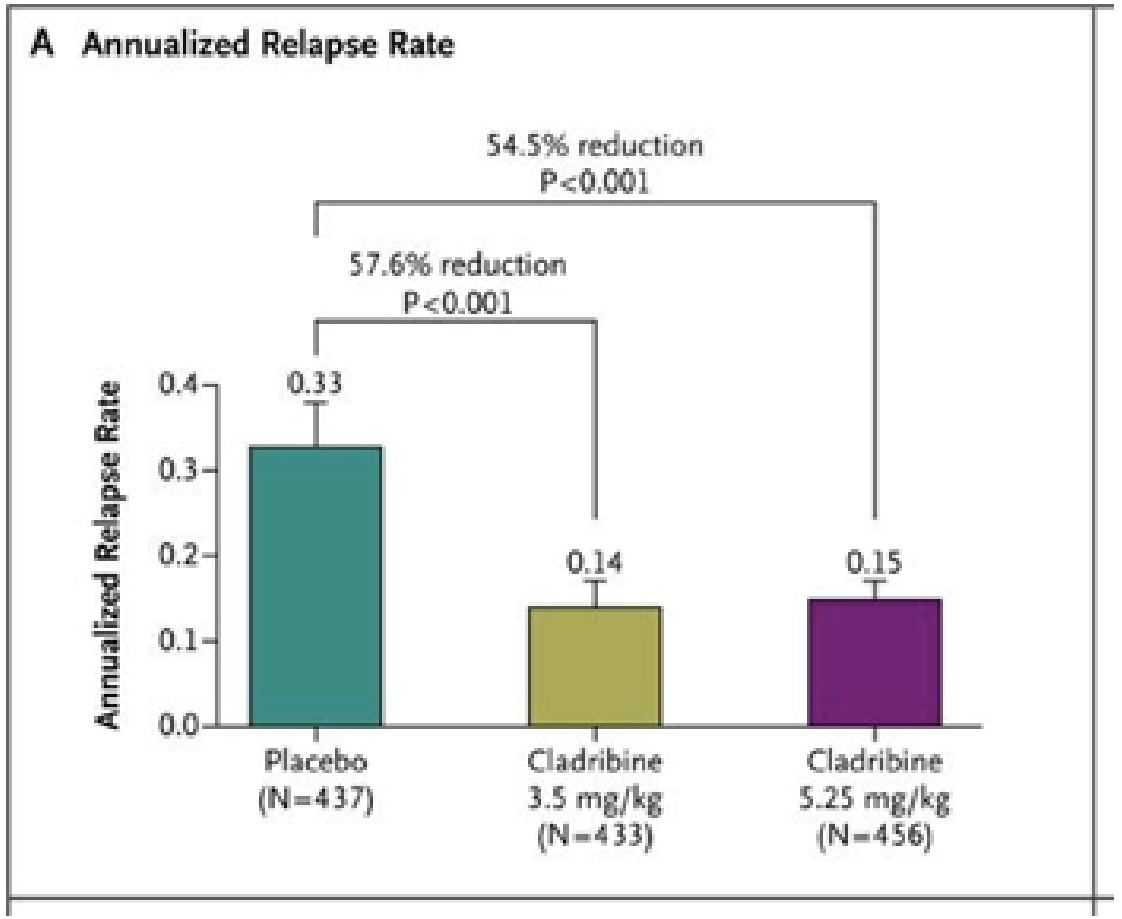
Cladribine

- Approved March 2019
  - RRMS and active SPMS
- MOA: Synthetic purine analog → DNA damage → cell apoptosis
  - T and B cells
- Dosing: 5 consecutive days month 1 and month 2 followed by repeat dosing in year two

CLARITY

Phase 3, double blind placebo-controlled

Primary end-point – annualized relapse rate



Giovannoni G, et al. N Engl J Med. 2010

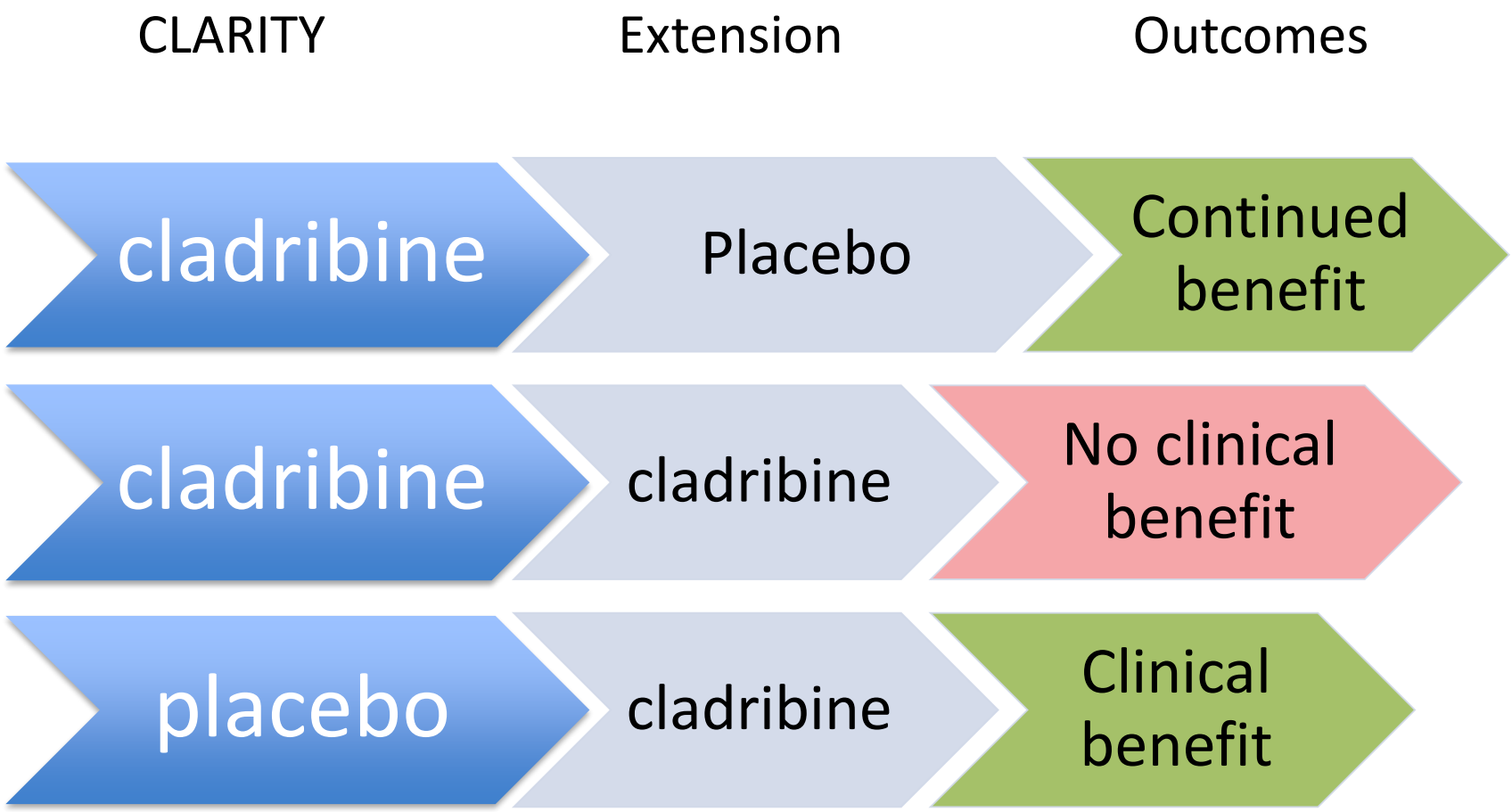
CLARITY - Safety

Table 3. Adverse Events and Investigator-Assessed Severity at 96 Weeks (Safety Population).

Adverse Event	Placebo (N=435)	Cladribine		
		3.5 mg/kg (N=430)	5.25 mg/kg (N=454)	Combined Doses (N=884)
Any adverse event — no. of patients (%)	319 (73.3)	347 (80.7)	381 (83.9)	728 (82.4)
Most common adverse events — no. of patients (%)*				
Headache	75 (17.2)	104 (24.2)	94 (20.7)	198 (22.4)
Lymphocytopenia	8 (1.8)	93 (21.6)	143 (31.5)	236 (26.7)
Nasopharyngitis	56 (12.9)	62 (14.4)	58 (12.8)	120 (13.6)
Upper respiratory tract infection	42 (9.7)	54 (12.6)	52 (11.5)	106 (12.0)
Nausea	39 (9.0)	43 (10.0)	50 (11.0)	93 (10.5)
Ratio of mild-to-moderate events to severe events*				
Headache	186:3	258:6	260:5	518:11
Lymphoctyopenia	11:0	118:5	180:15	298:20
Nasopharyngitis	95:0	107:0	91:0	198:0
Upper respiratory tract infection	80:0	118:0	99:1	217:1
Nausea	48:1	73:1	68:1	141:2
Any serious adverse event — no. of patients (%)	28 (6.4)	36 (8.4)	41 (9.0)	77 (8.7)
Infections and infestations†	7 (1.6)	10 (2.3)	13 (2.9)	23 (2.6)
Neoplasms (benign, malignant, and unspecified)‡	0	6 (1.4)	4 (0.9)	10 (1.1)
Death§	2 (0.5)	2 (0.5)	2 (0.4)	4 (0.5)

Giovannoni G, et al. N Engl J Med. 2010

CLARITY – 2 Year Extension

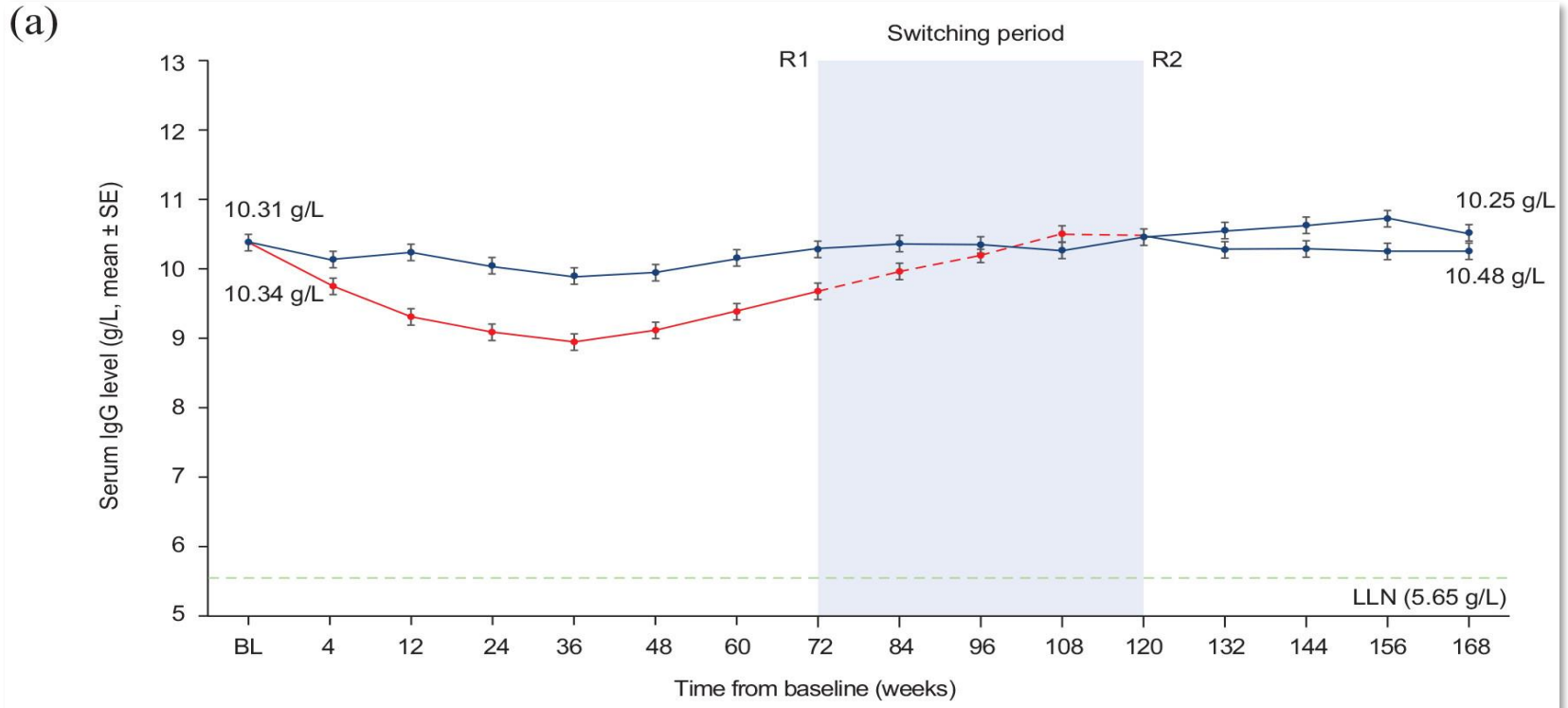


Giovannoni G, et al. *Mult Scler*. 2018

Ofatumumab

- Approved in August 2020
  - CIS, RRMS, active SPMS
- MOA: monoclonal antibody targeting CD20 → selective B cell depletion
- Dosing: SubQ injection – 20 mg at week 0, 1 and 2 followed by 20 mg monthly
- Pre-labs: CBC, CMP, HBV serology, quantiferon, serum immunoglobulins
- Adverse events: similar to other CD20 agents

Ofatumumab - ALITHIOS



No. of patients at visit

Continuously treated ofatumumab	1269	1233	1248	1219	1180	1132	1083	902	961	758	712	602	514	469	345	241
Teriflunomide/ ofatumumab	675	672	673	666	672	669	666	670	635	634	635	567	499	447	350	215
Before/ after switch	675	672	673	666	672	669	666	664/ 6	477/ 158	313/ 321	167/ 468	72/ 495	499	447	350	215

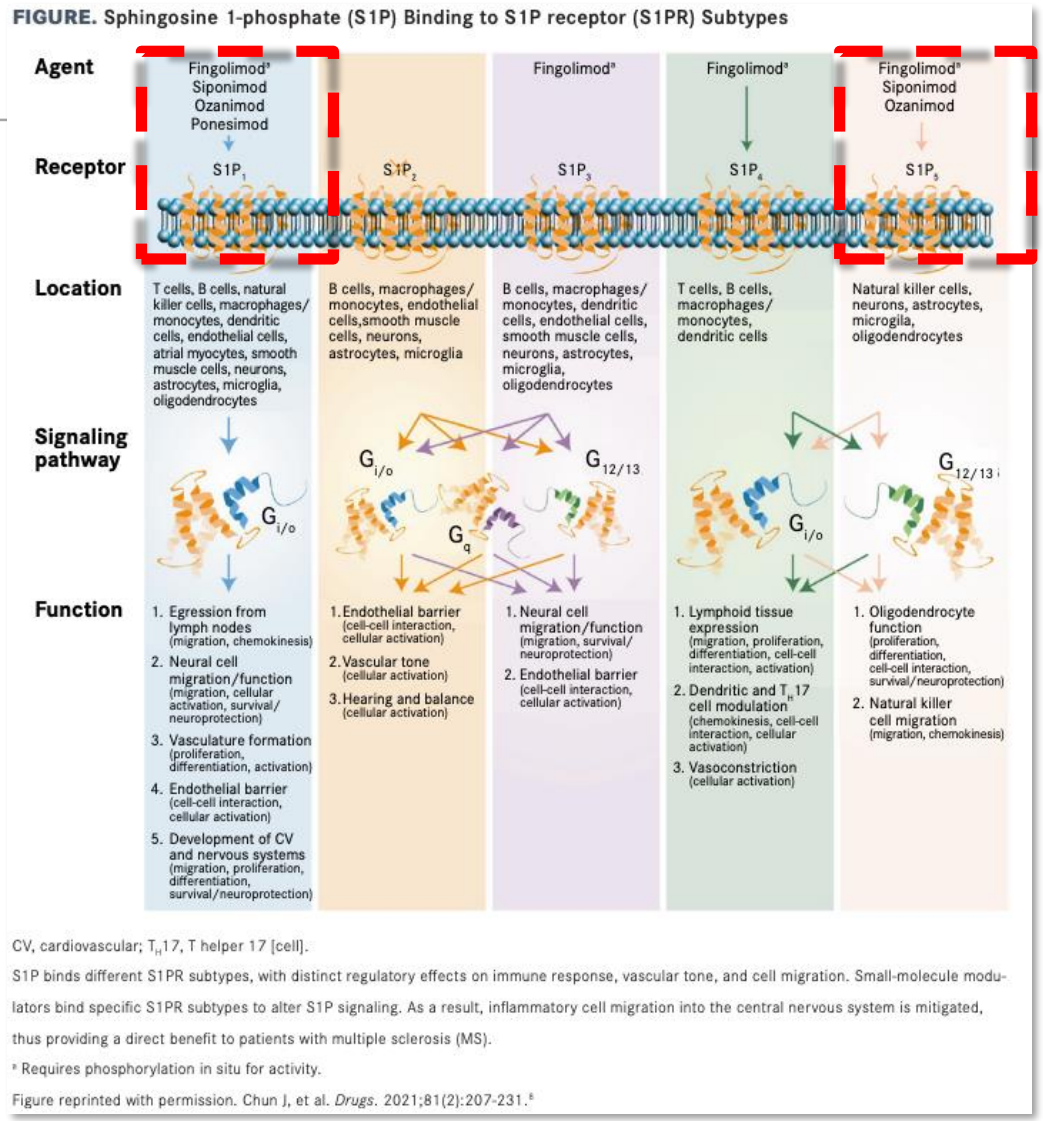
Hauser SL, et al. *Mult Scler.* 2022

Diroximel fumarate

- Approved in October 2020
  - RRMS, CIS, active SPMS
- Diroximel fumarate → monomethyl fumarate
- Less GI side effects than dimethyl fumarate
- Trial was about adverse side effects NOT efficacy

Siponimod

- Approved March 2019
  - RRMS, active SPMS
- MOA: selective sphingosine 1-phosphate receptor modulator
- Dosing: Titrate to 1 mg or 2 mg daily



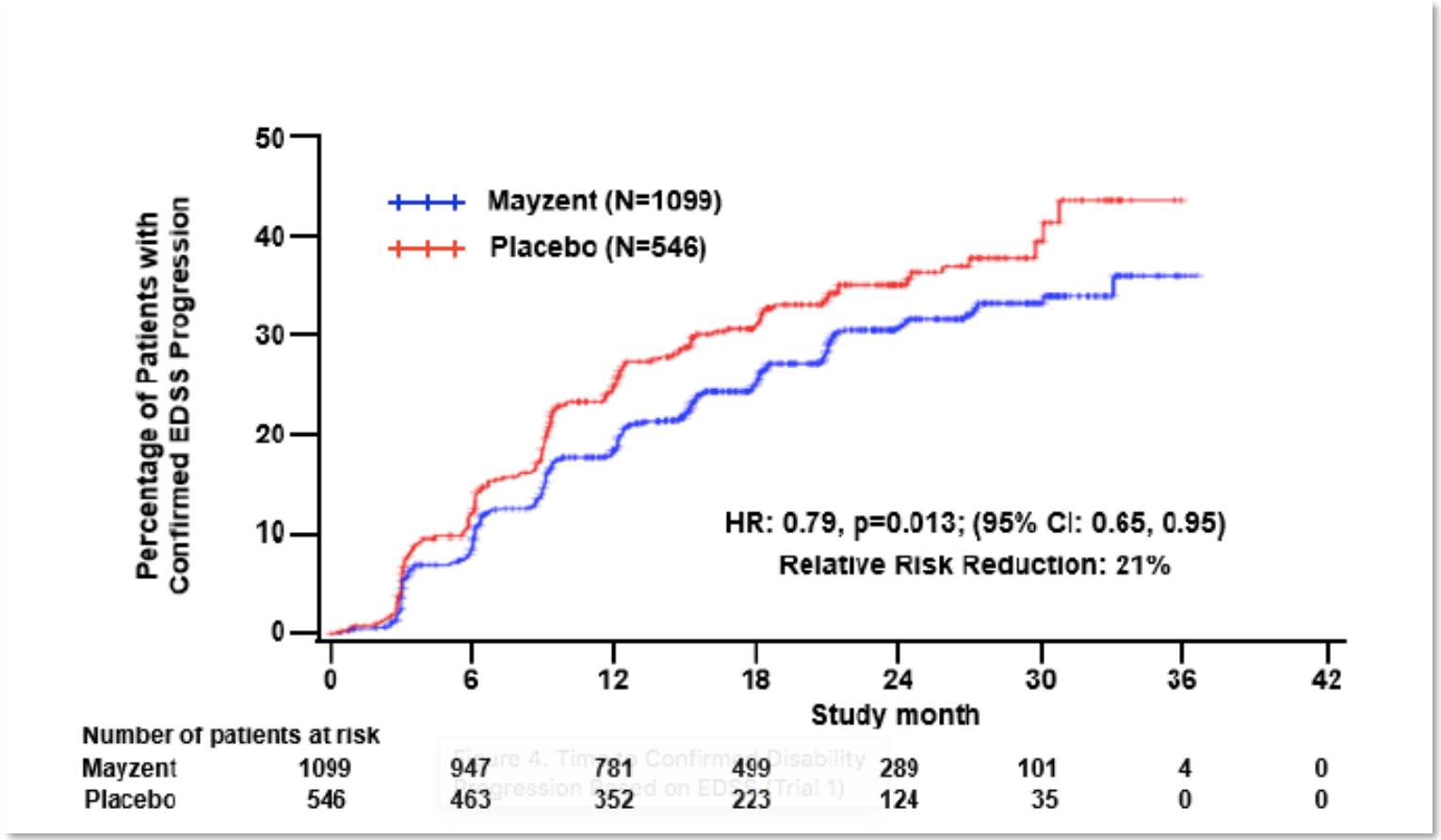
Chun J, et al. *Drugs*. 2021;81(2):207-231

Siponimod

- Prelabs - CYP2C9 genotype, CBC, LFTs, VZV, ECG, OCT
  - Different dosing/titration regimens based on genotype
    - Contraindicated in CYP2C9*3/*3 genotype
- Monitoring
  - CBC, LFTs

EXPAND – Siponimod in SPMS

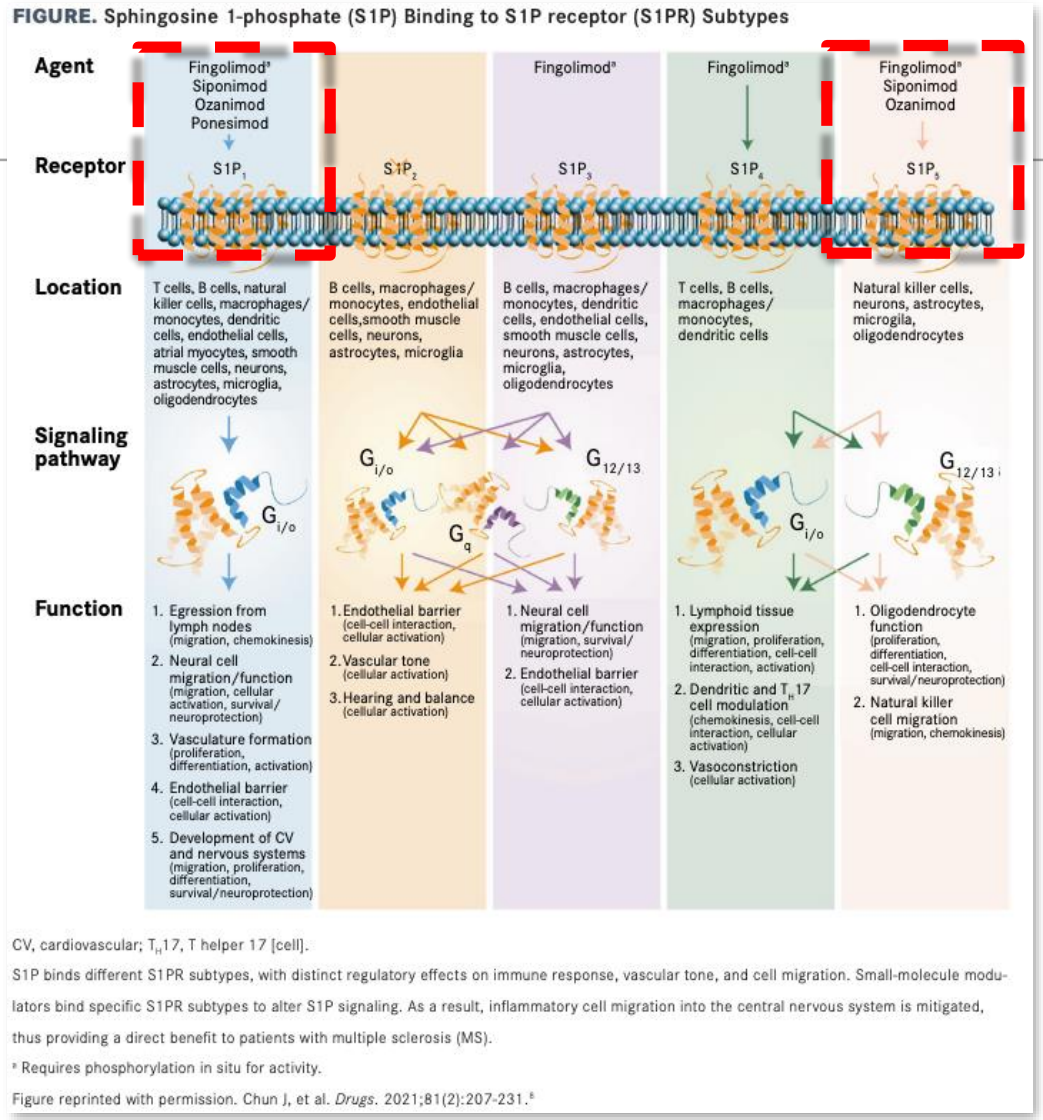
- Siponimod vs Placebo
  - Confirmed disability progression



Kappos L, et al. *Lancet*. 2018

Ozanimod

- Approved March 2020
- Approved for RRMS, CIS and active SPMS
- MOA - Selective $S1P_1$ and $S1P_5$ receptor modulator
- Once daily pill
  - 7 day titration on initiation
    - 0.23 mg → 0.46 mg → 0.92 mg



Chun J, et al. *Drugs*. 2021;81(2):207-231

Ozanimod - SUNBEAM

- Randomized, double-blind, double-dummy, active-controlled phase 3 trial
- Ozanimod vs interferon beta-1a
- Primary end point – annualized relapse rate
  - 48% reduction in ARR

*** Smaller losses of whole brain volume, cortical grey matter volume and thalamic volume noted in patients treated with ozanimod

Comi G., et al. *Lancet Neurol.* 2019

Ozanimod – Cognitive Processing Speed

- Post-hoc analysis
  - Improved Single Digit Modality Test (SDMT) scores at months 6 and 12 noted in patients treated with ozanimod
    - Noted improvement in scores in 30% of patients on ozanimod vs 22.2% of patients on interferon beta-1a
- Open label extension (DAYBREAK)
  - 77% of patients improved or remained stable at 3 years

Comi G., et al. *Lancet Neurol.* 2019
Cree BA., et al. *Mult Scler.* 2022

Ozanimod - Safety

- Most commonly experienced AEs included nasopharyngitis, upper respiratory tract infections, and headache

- No clinically significant bradycardia or 2nd/3rd degree AV block noted

Ozanimod

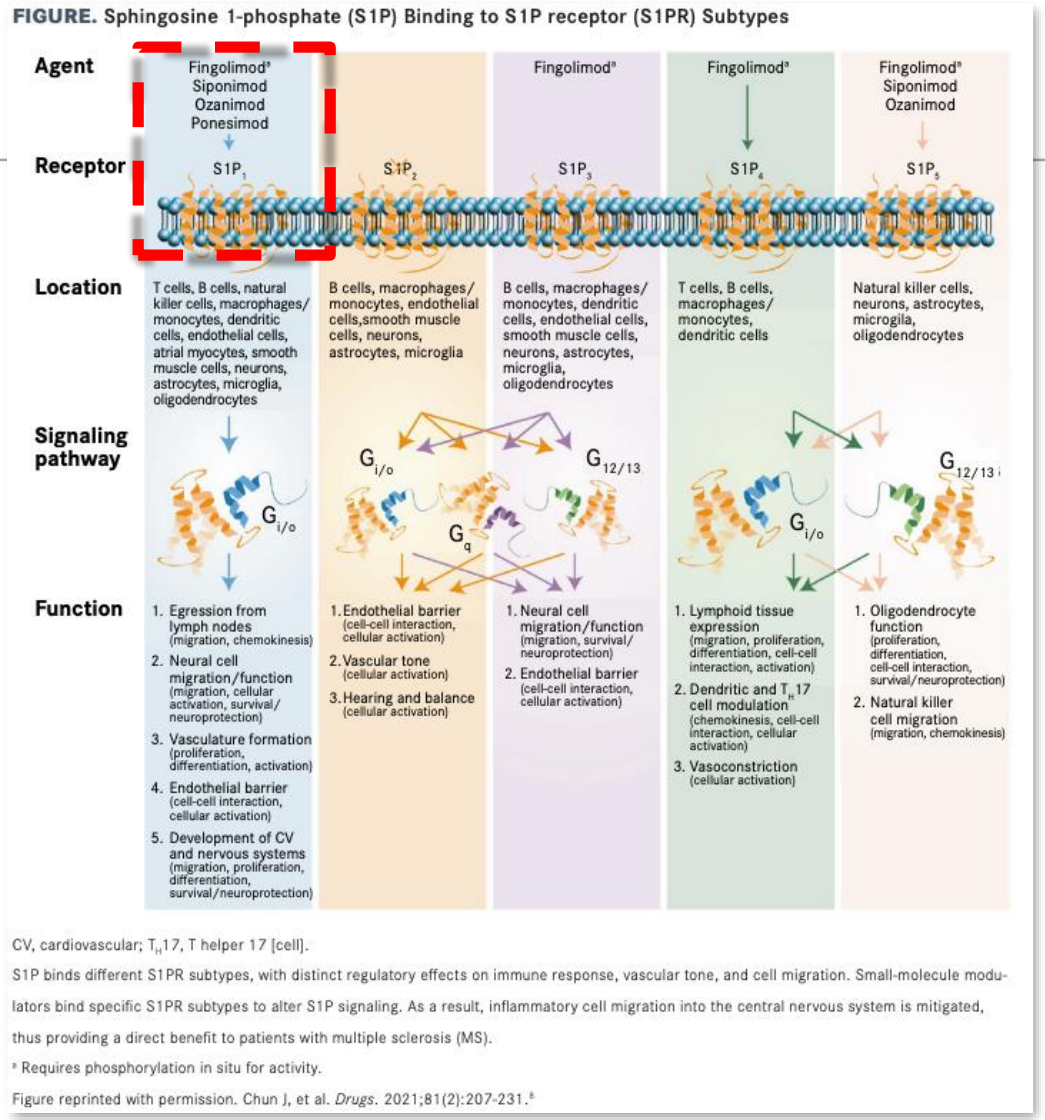
- No first dose monitoring required
- No genetic testing required
- Possible Interactions:
  - MAOIs
  - Tyramine containing food/beverages
  - SSRI/SNRIs
  - CYP2C8 inhibitors

Ponesimod

- Approved March 2022
- Approved for RRMS, CIS, active SPMS
- Once daily pill
  - Titration recommended for the first 2 weeks of treatment
    - 2 mg →→→→ 20 mg

Ponesimod

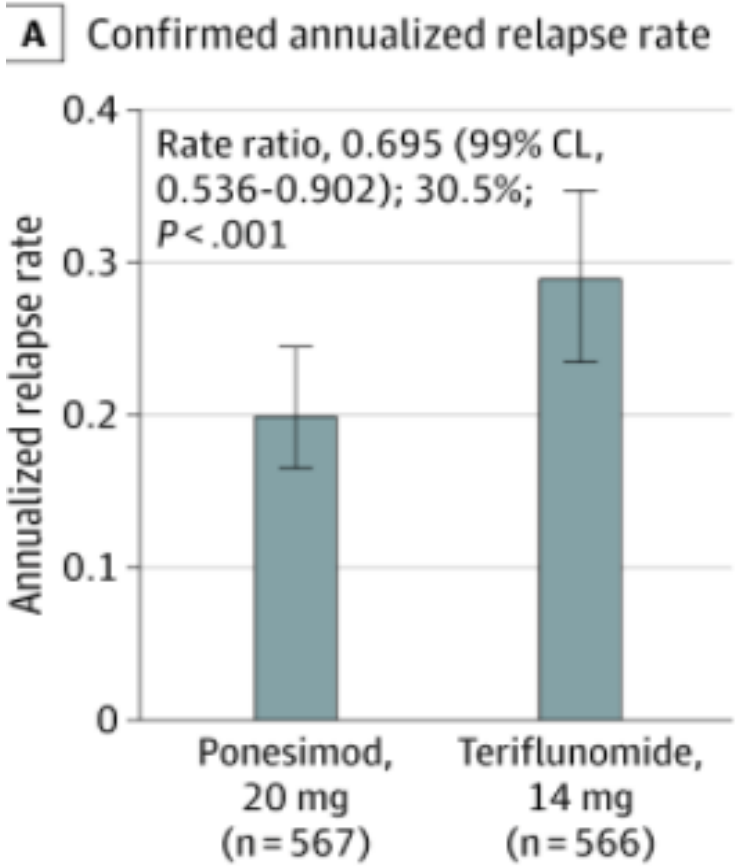
- Selective, rapidly reversible $S1P_1$ receptor modulator
- Blocks egression of lymphocytes from the lymphoid tissues



Chun J, et al. *Drugs*. 2021;81(2):207-231

Ponesimod - OPTIMUM

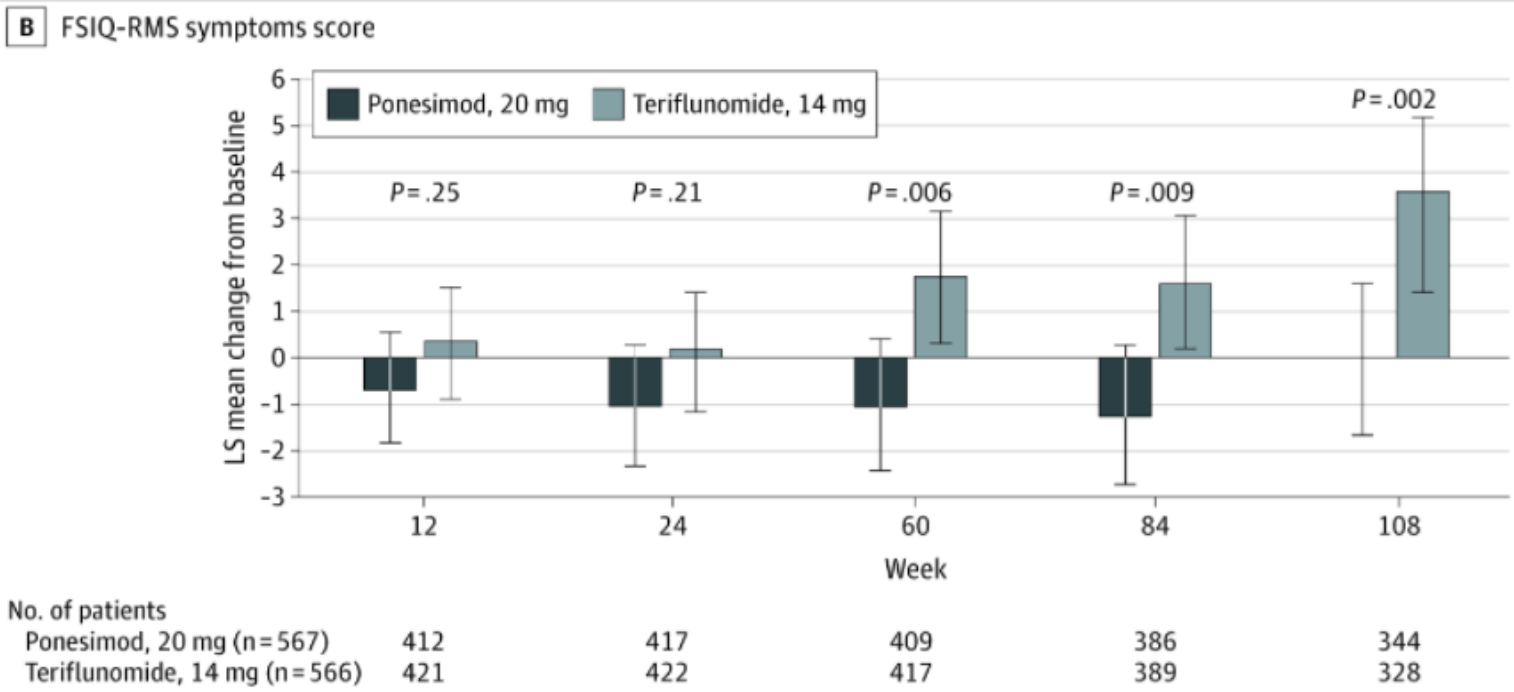
- Phase 3, multicenter, randomized, double-blind, active-comparator superiority study
  - Ponesimod vs teriflunomide
  - Primary End Point
    - Annualized relapse rate reduction of 30.5%



Kappos L, et al. JAMA Neurol. 2021

Ponesimod - OPTIMUM

- Secondary end-point of interest
  - Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis



Kappos L, et al. JAMA Neurol. 2021

Ponesimod - Safety

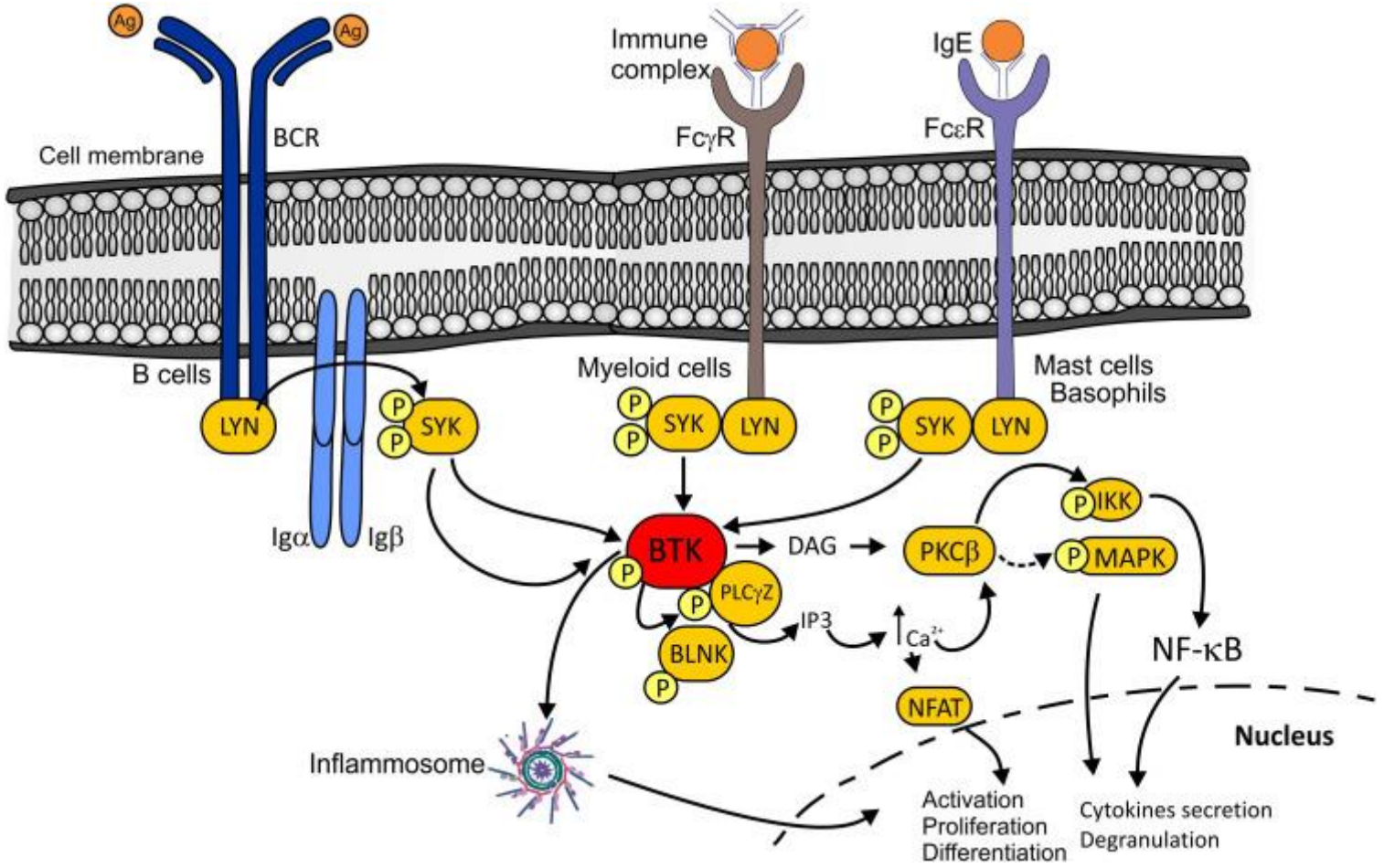
- Increased ALT
- Upper respiratory tract infections
- Headache
- No clinically significant $2^{nd}/3^{rd}$ degree heart block

Ponesimod

- Unique features compared to other S1PR modulators
  - No first dose monitoring
  - No genetic testing
  - No food interactions
  - No interactions with SSRIs

MS on the Horizon

Bruton Tyrosine Kinase Inhibitors (BTKis)



Evobrutinib
Tolebrutinib
Fenebrutinib
Orelabrutinib

Carnero Contentti E, et al. Drug Des Devel Ther. 2022

MS Treatments on the Horizon

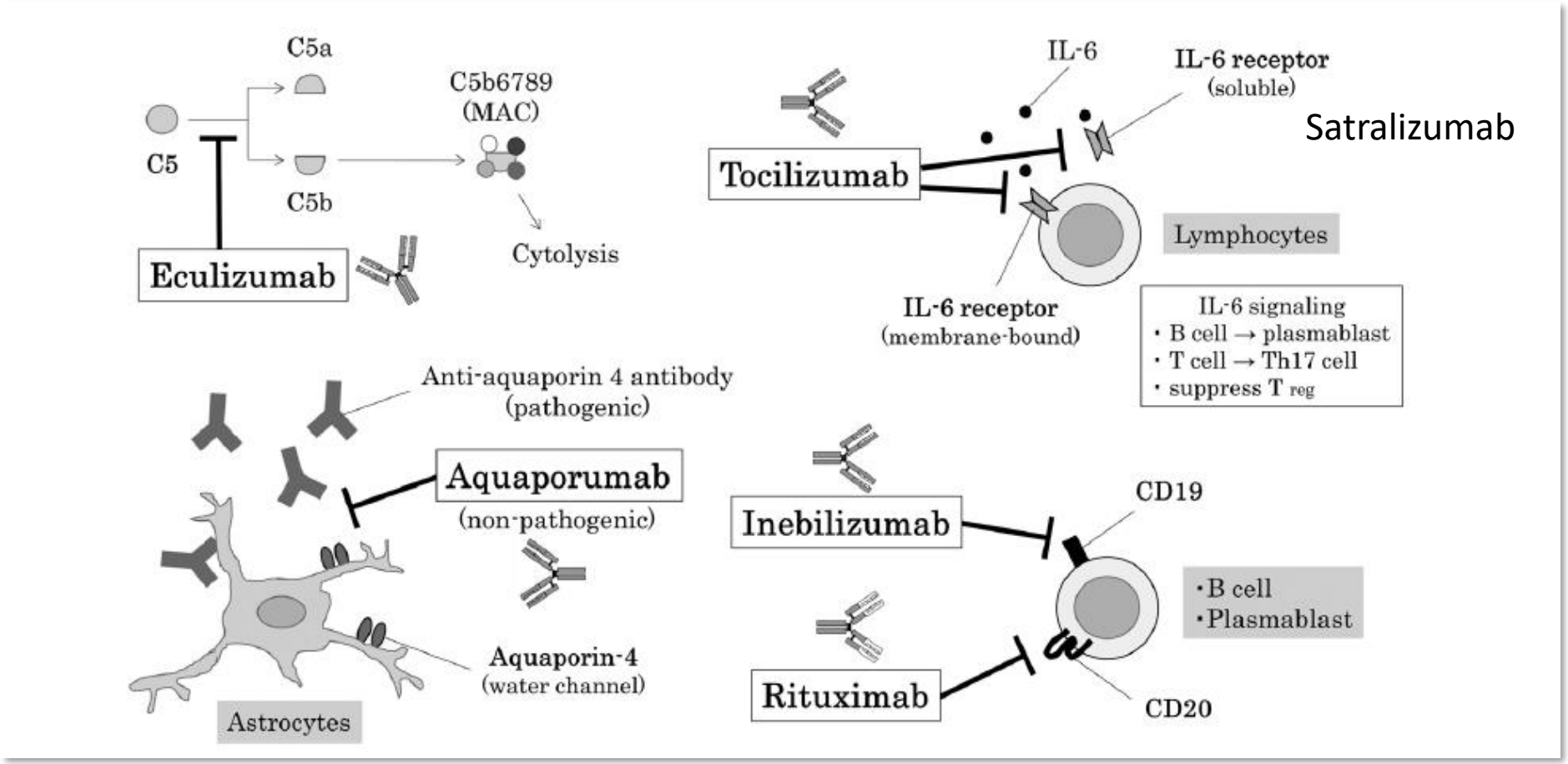
- **ATA188**
  - EBV targeted T cell immunotherapy
  - Progressive MS
- **ANK-700**
  - Myelin antigen
  - RRMS

NMOSD

NMOSD Treatment Landscape

- No FDA approved medications until June 2019
- Off label uses
  - Mycophenolate mofetil
  - Azathioprine
  - Rituximab

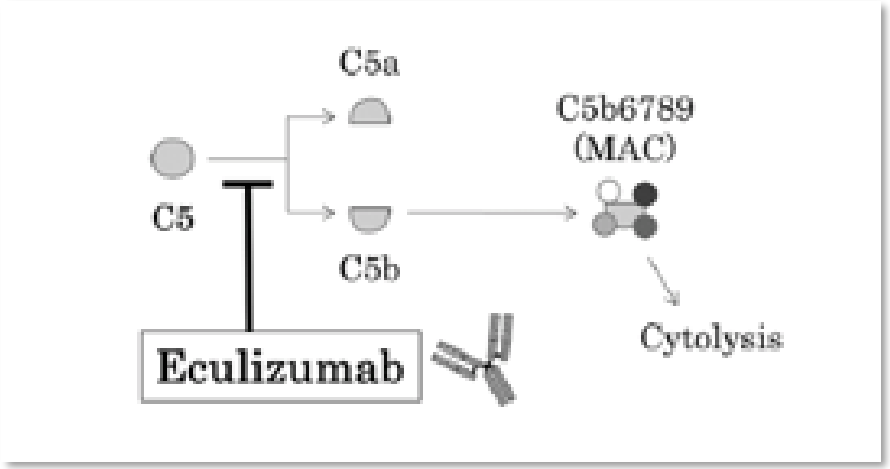
2019 →



Akaishi et al, 2017

Eculizumab

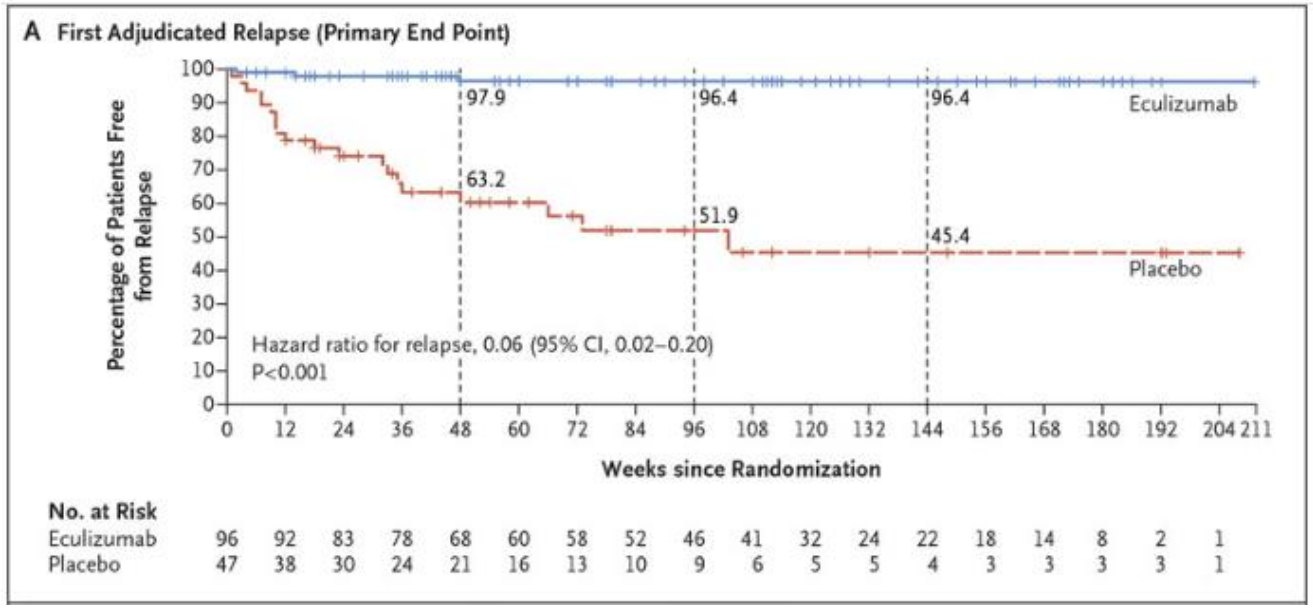
- Approved June 2019
- Humanized monoclonal antibody against terminal complement protein C5
  - Inhibits cleavage of C5 into C5a and C5b-9 complex (MAC)
- Menigococcal vaccine!
- Dosing: 900 mg weekly x 4 weeks followed by 1200 mg every two weeks



Akaishi et al, 2017

Eculizumab

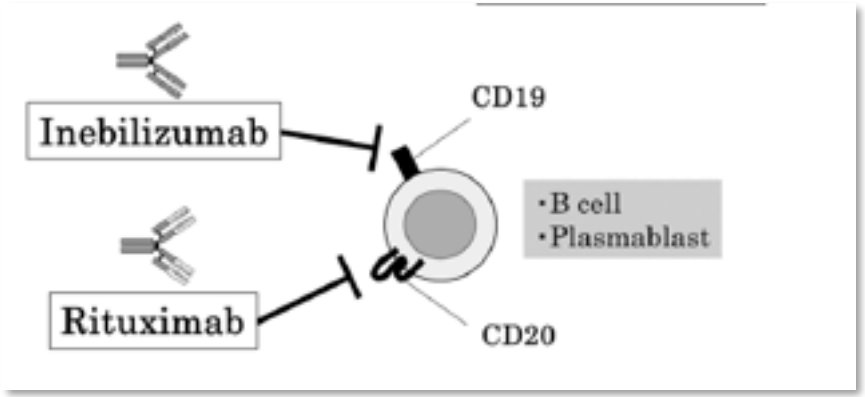
- PREVENT trial
  - Eculizimab vs placebo
    - Week 48 – 97.9% of treated relapse free vs 63.2% in placebo
    - Many of these patients were on concomitant immunotherapy



Pittock SJ, et al. N Engl J Med. 2019

Ineblizumab

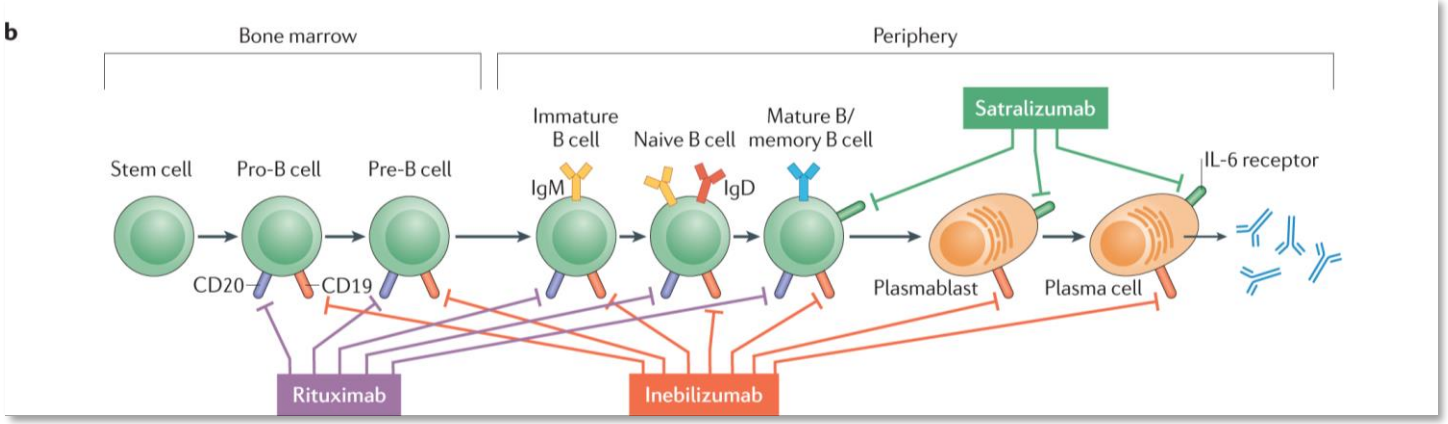
- Approved June 2020
- Humanized monoclonal ab against CD19
  - Broader depletion of B-cells than CD20 agents
- Dosing: 300 mg on day 1 and 15 and then Q6 months
- N-Momentum
  - AQP+ and AQP4 - patients
  - Inebilizumab (monotherapy) vs placebo
    - 77% reduction in risk of relapse



Akaishi et al, 2017

Satralizumab

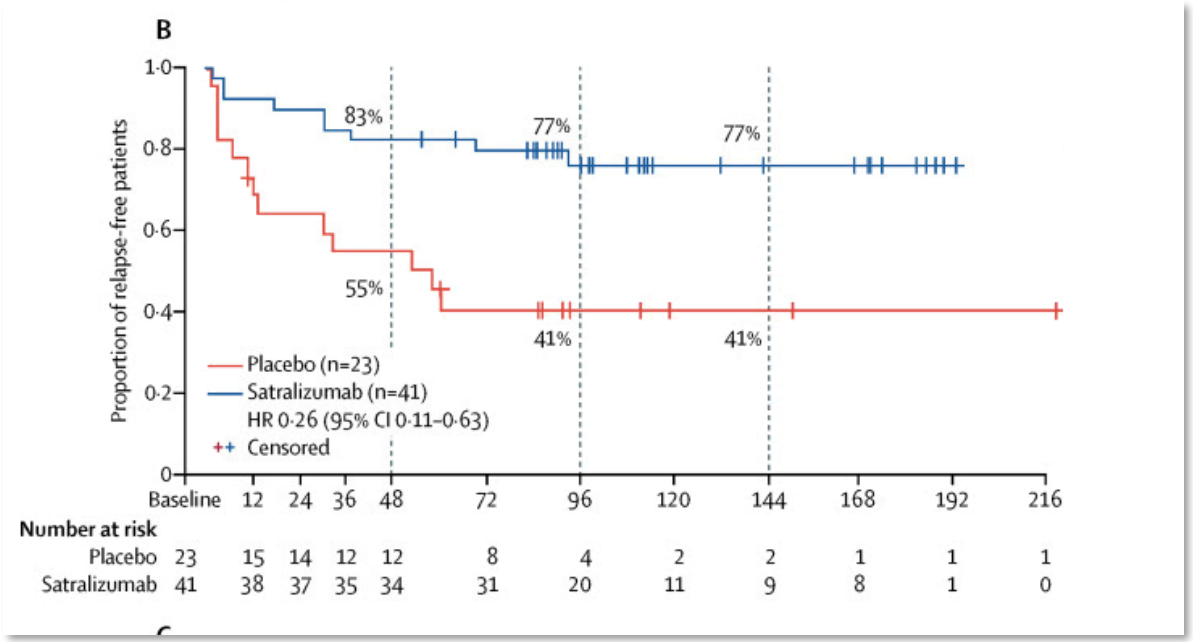
- Approved August 2020
- Humanized monoclonal antibody against IL-6 receptor
- Dosing: 120 mg SQ at week 0, 2 and 4 followed by every 4 weeks



Pittock, S.J., et al. *Nat Rev Neurol*. 2021

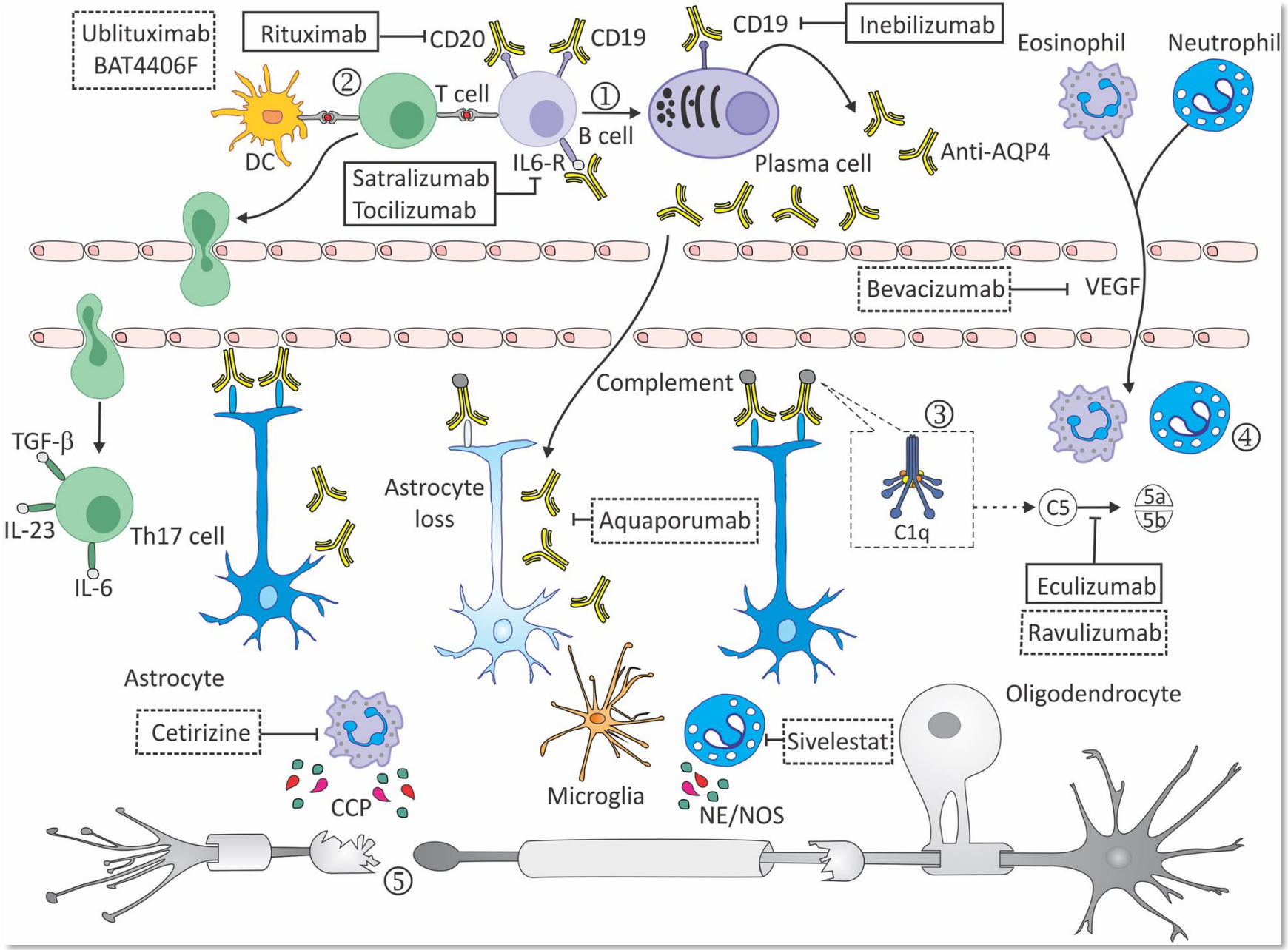
Satralizumab

- **SAKuStar**
  - Satralizumab vs placebo
  - AQP4 + and – patients
  - Time to first relapse – 76% vs 62%
    - Improved to 83% vs 55% in AQP4+



Traboulsee A, et al. Lancet Neurol. 2020

NMOSD on the Horizon



Carnero Contentii, E, et al. *J Neuroinflammation.* 2021

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END – extra template slide

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Question

- Year 2 of cladribine should not be completed if absolute lymphocyte count is less than
  a) 500
  b) 800
  c) 1000
  d) 1500

Question

- Year 2 of cladribine should not be completed if absolute lymphocyte count is less than
  a) 500
  b) 800
  c) 1000
  d) 1500

Question

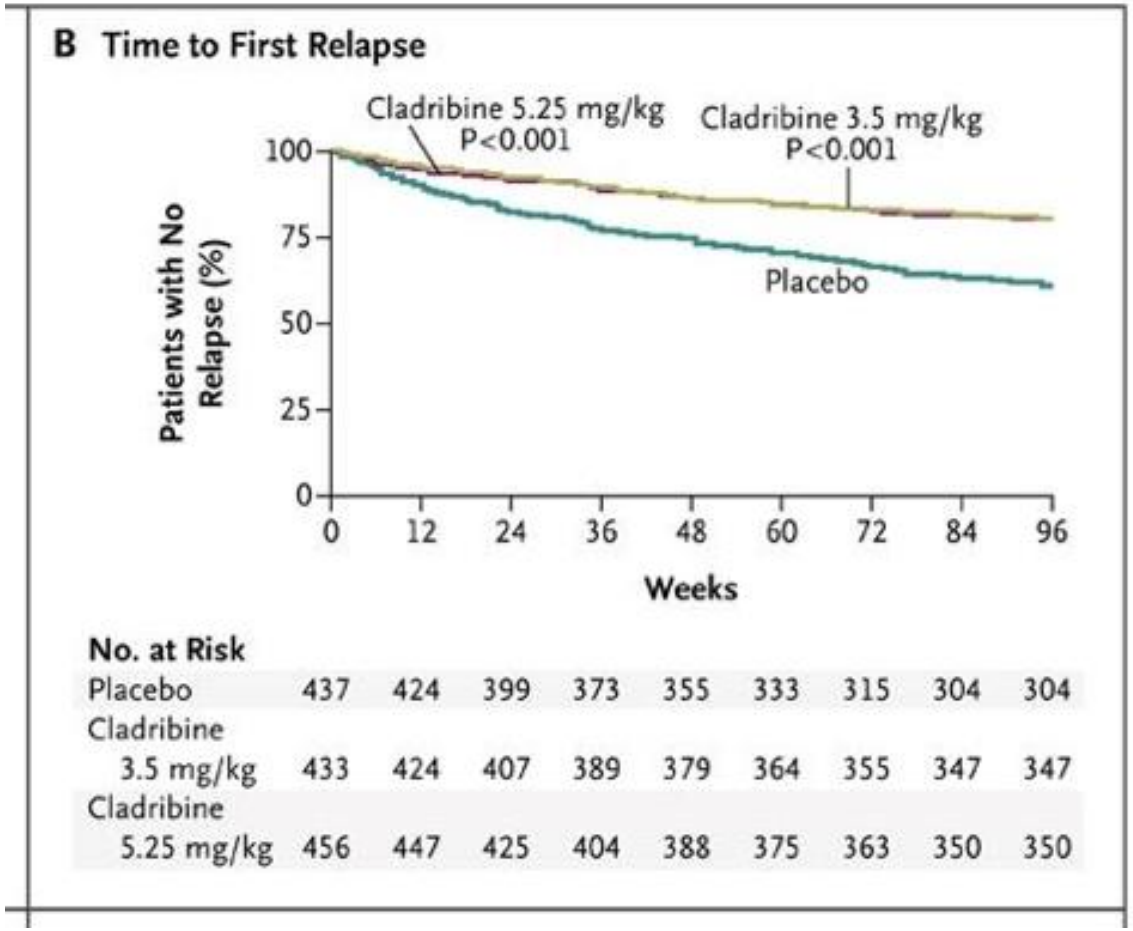
- All S1P receptor modulators require first dose observation?
  a) True
  b) False

Question

- All S1P receptor modulators require first dose observation?
  a) True
  b) False

CLARITY

- Secondary end-points
  - Time to 1st relapse



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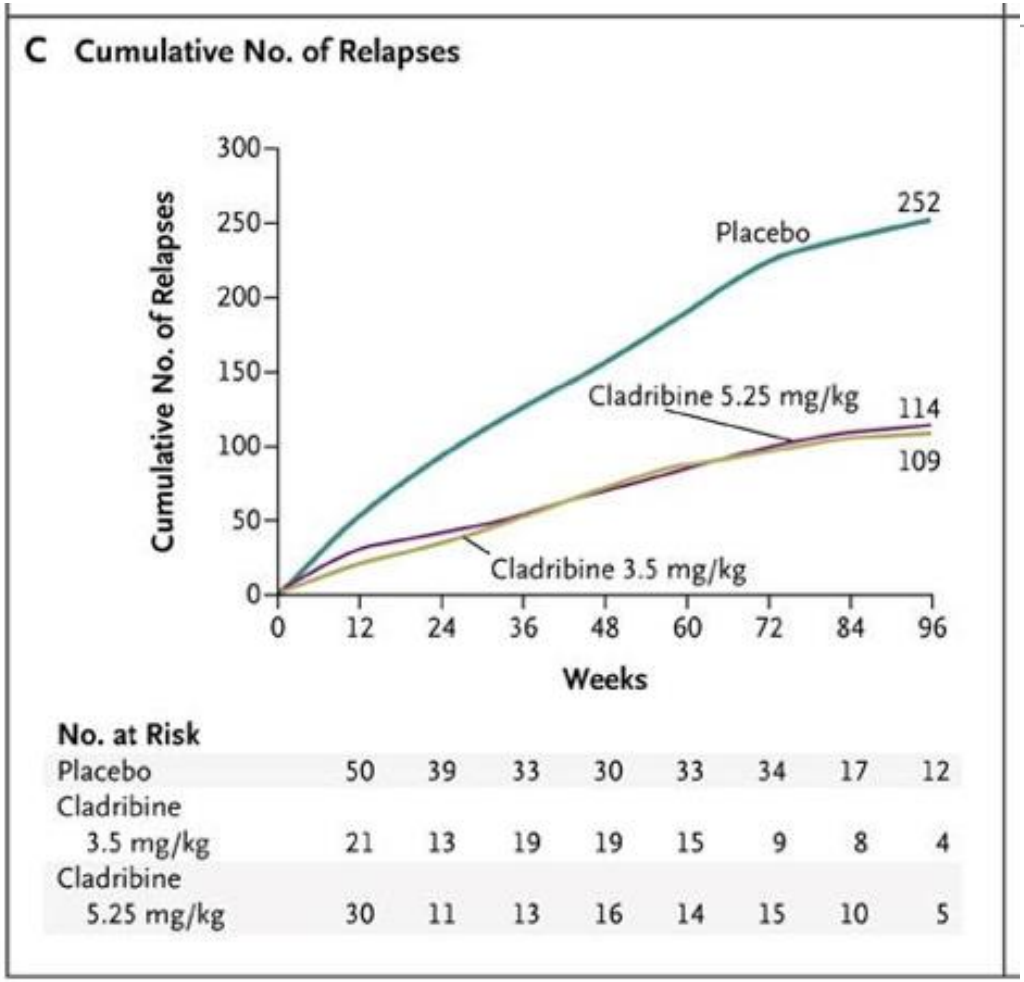
CLARITY

- Secondary end-points
  - Time to 1st relapse
  - Cumulative number of relapses



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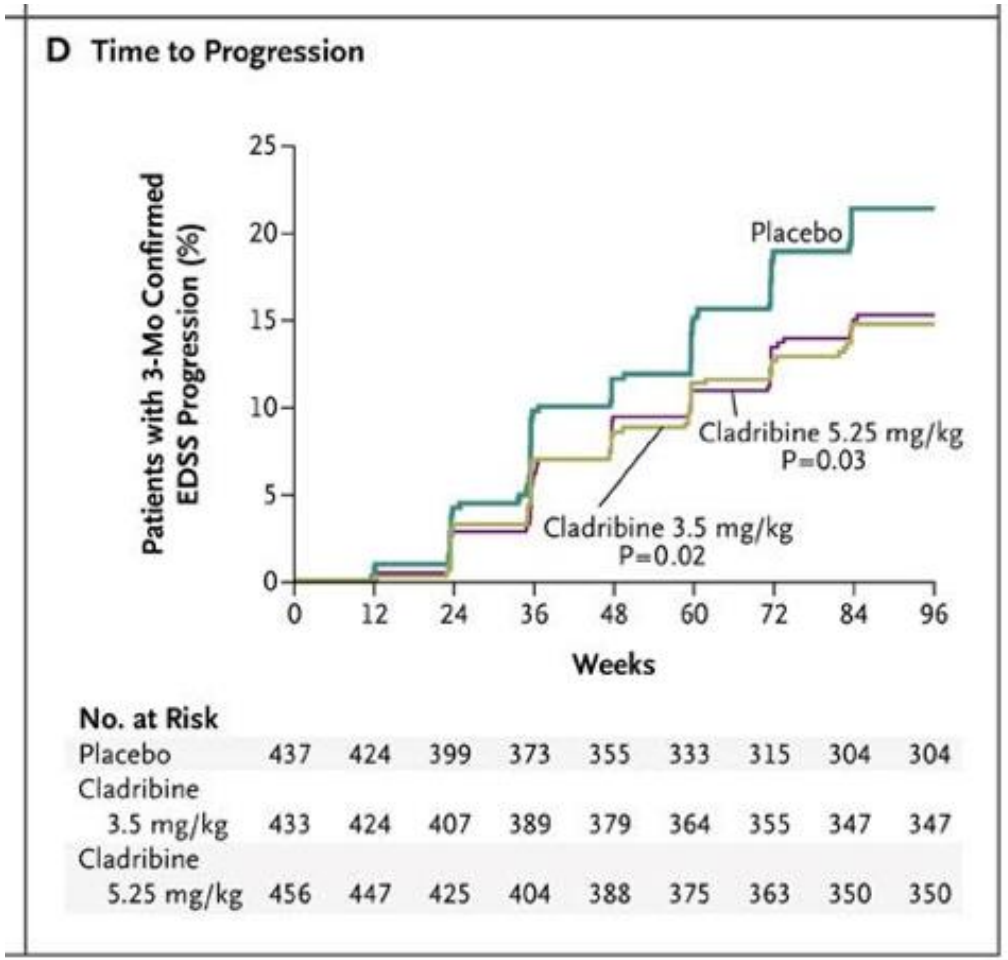
CLARITY

- Secondary end-points
  - Time to 1st relapse
  - Cumulative number of relapses
  - Time to progression



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