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BTK Inhibitors:
An Emerging Target in Multiple Sclerosis

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Faculty

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Dr. Reich is Chief, Translational Neuroradiology Section, National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), USA. He appears here in his private capacity, as an approved Outside Activity, and the views and opinions here do not represent those of NINDS or NIH.

Faculty Disclosures

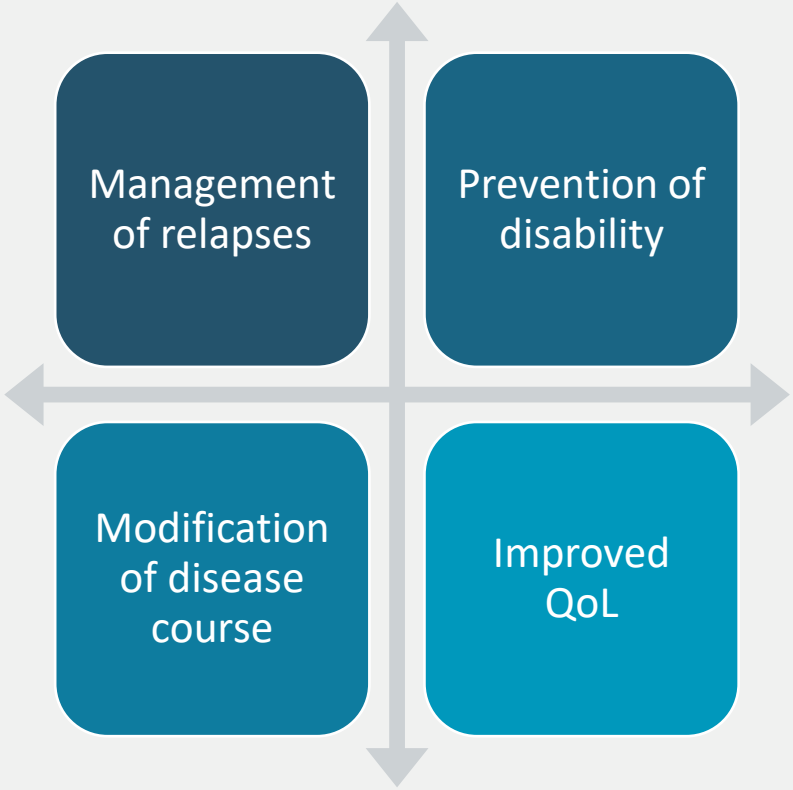
Daniel S. Reich, MD, PhD

Collaborative Research: Abata Therapeutics, Sanofi

Learning Objectives

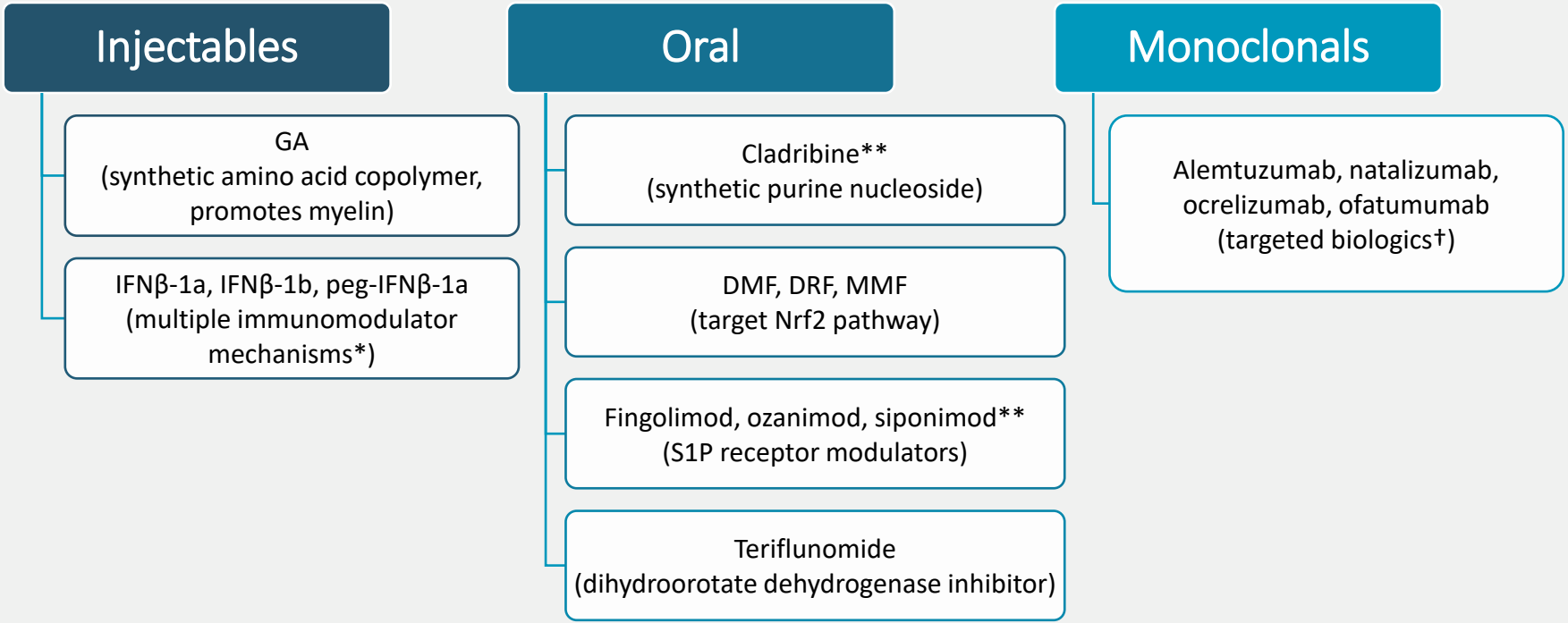
- Improve knowledge of clinicians on the role of Bruton's tyrosine kinase (BTK) inhibition in multiple sclerosis (MS) management
- Describe the mechanisms of action for emerging BTK inhibitors
- Recall available safety and efficacy data for emerging BTK inhibitors

Goals of Therapy in MS



MS, multiple sclerosis; QoL, quality of life.

Currently Approved MS Treatments



*Inhibition of T-cell activation, T-cell proliferation, and leukocyte migration across the blood-brain barrier; induction of apoptosis of autoreactive T cells and regulatory T cells; and cytokine modulation; **Cladribine and siponimod approved specifically for active SPMS; †Alemtuzumab, anti-CD-52; natalizumab, anti-α4β1-integrin; and ocrelizumab and ofatumumab, anti-CD20.

DMF, dimethyl fumarate; DRF, diroximel fumarate; GA, glatiramer acetate; IFN, interferon; MMF, mycophenolate mofetil; Nrf2, nuclear factor erythroid 2-related factor 2; S1P, sphingosine-1-phosphate; SPMS, secondary progressive multiple sclerosis.

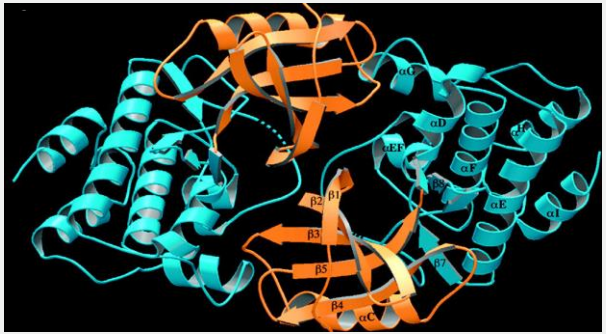
Current Unmet Needs in Treatment

- Greater prevention of disability accumulation
- CNS neuroprotection
- CNS repair
- Highest efficacy oral therapies

CNS, central nervous system.

Overview of BTK

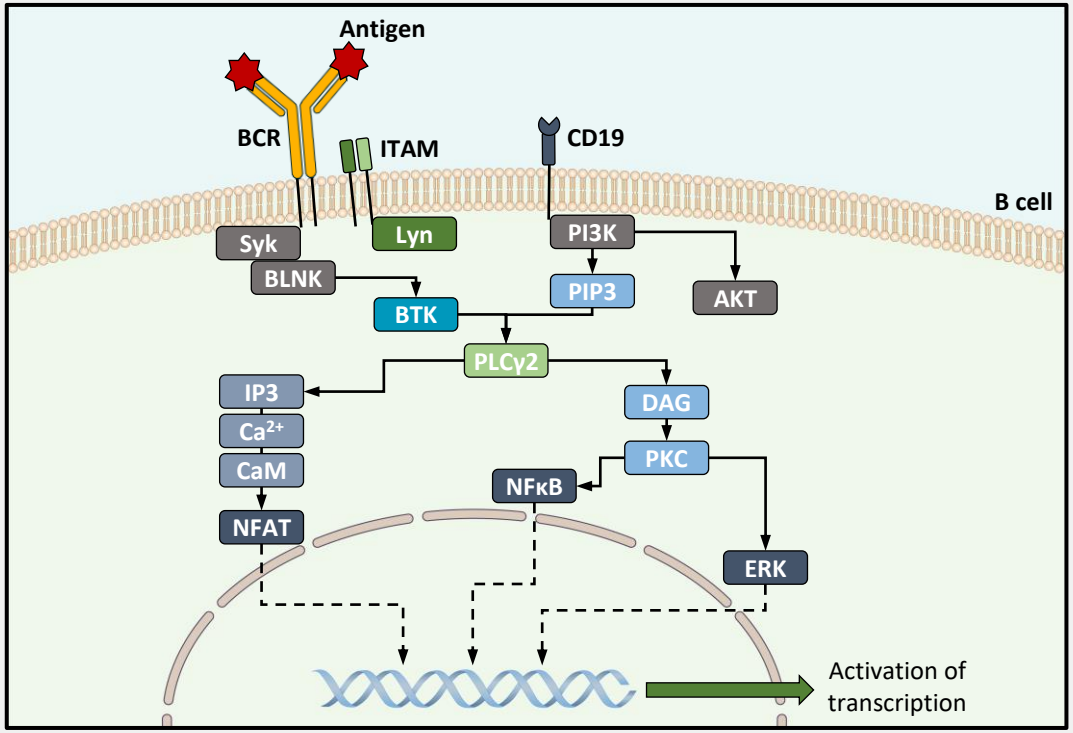
- Cytoplasmic non-receptor protein-tyrosine kinase belonging to the TEC family
- Crucial signaling protein linking BCR signals to B-cell proliferation, differentiation, and survival
- Expressed in almost all cells of hematopoietic lineage, except T cells and plasma cells
- Driving factor in lymphoproliferative disorders, autoimmune diseases, and response to infection



BCR, B-cell receptor; BTK, Bruton's tyrosine kinase.

McDonald C et al. *Immunology.* 2021;164(4):722-736; Neys SFH et al. *Drugs.* 2021;81(14):1605-1626; Reich DS et al. *Lancet Neurol.* 2021;20(9):729-738.

The Role of BTK in B-Cell Development and Activity

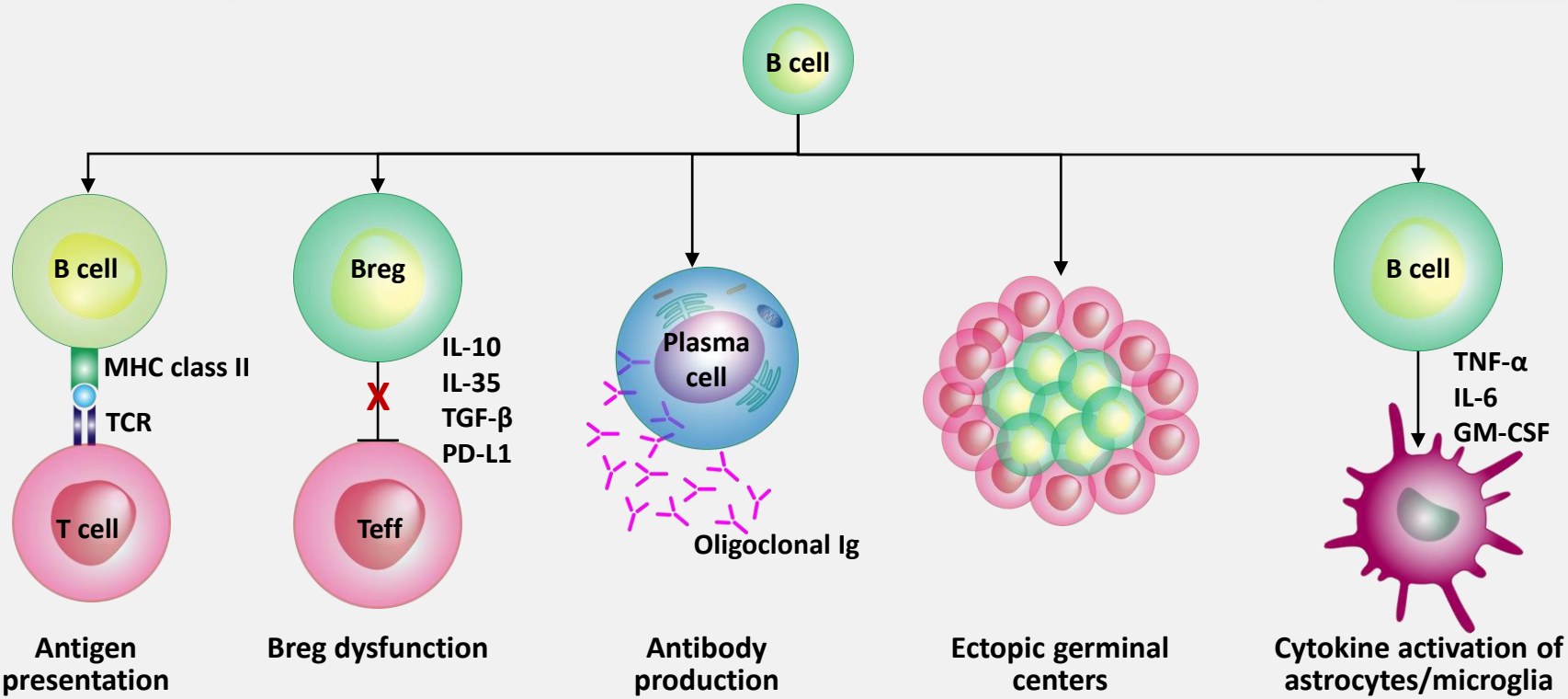


- Cell proliferation, differentiation, and survival
- Antigen presentation
- Cytokine production
- Antibody production

AKT, protein kinase B; BLNK, B-cell linker protein; CaM, calmodulin; DAG, diacylglycerol; ERK, extracellular signal-regulated kinase; IP3, inositol triphosphate; ITAM, immunoreceptor tyrosine-based activation motif; NFAT, nuclear factor of activated T cells; NFκB, nuclear factor-κB; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PLCγ2, phospholipase C-γ.

McDonald C et al. *Immunology.* 2021;164(4):722-736.

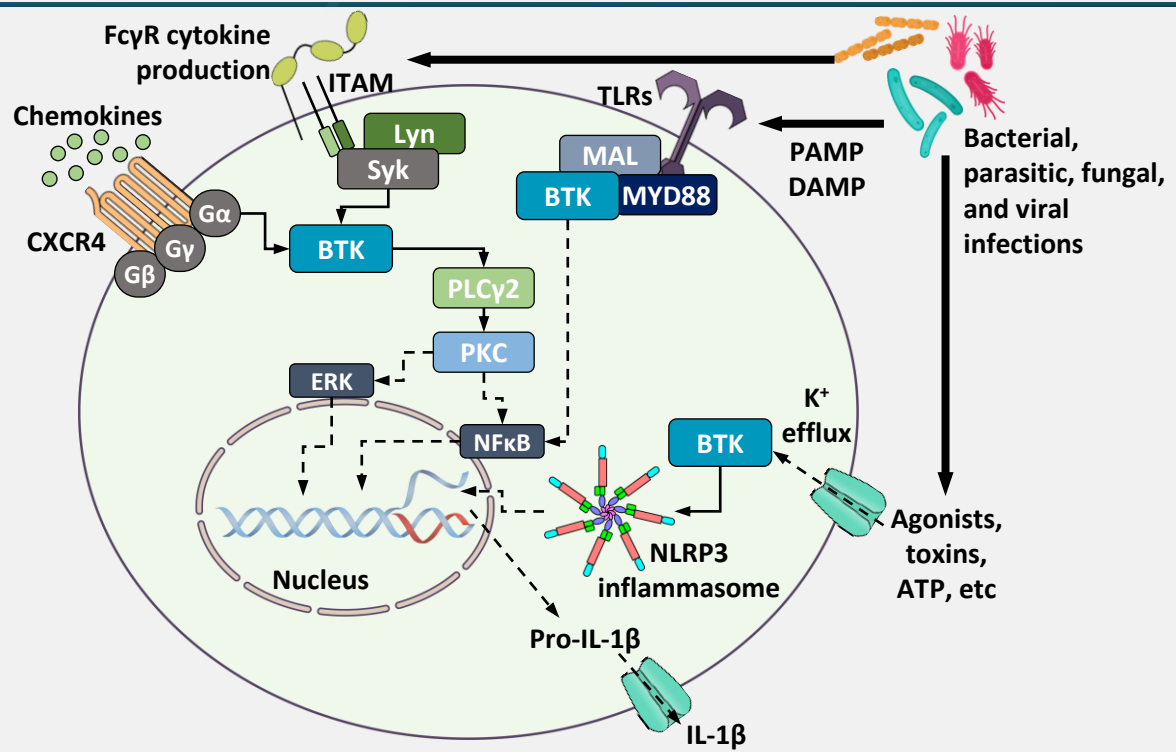
B Cells in MS



Breg, regulatory B cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; PD-L1, programmed cell death ligand 1; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α.

Baecher-Allan C et al. *Neuron.* 2018;97(4):742-768.

The Role of BTK in Innate Immunity

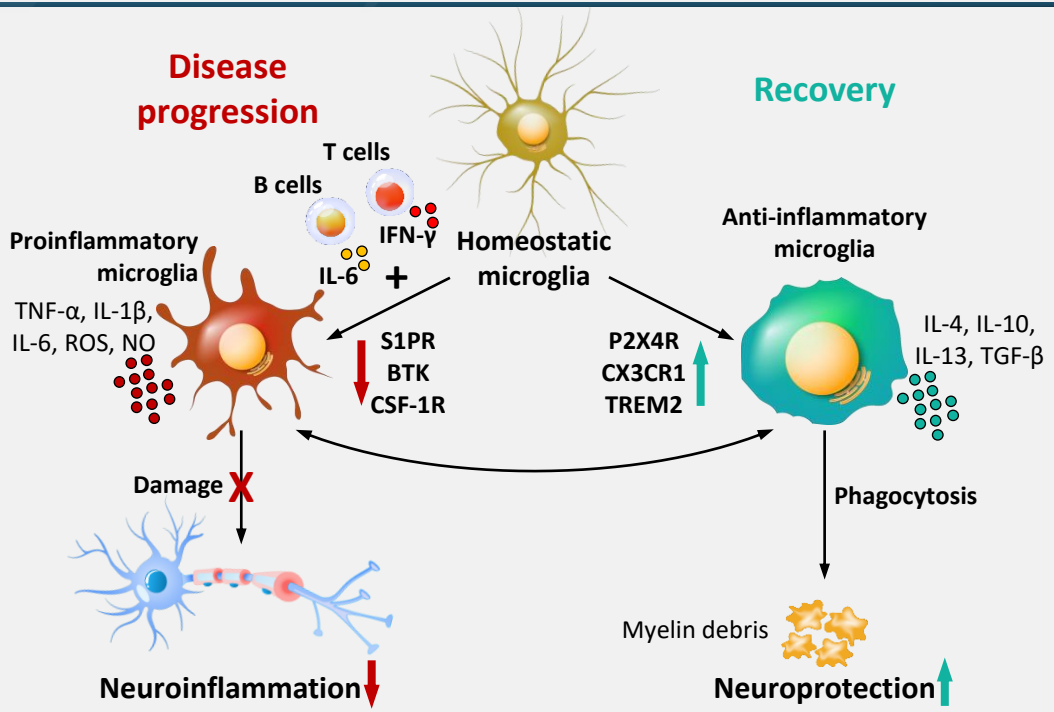


- Participate in CXCR4-, FcγR-, and TLR-mediated signaling in myeloid cells
- Influence myeloid phenotype and downstream proinflammatory cytokine production

ATP, adenosine triphosphate; CXCR4, CXC chemokine receptor 4; DAMP, damage associated molecular pattern; FcγR, Fc receptor; MAL, MYD88 adaptor-like; MYD88, myeloid differentiation primary response 88; NLRP3, NLR family pyrin domain containing 3; PAMP, pathogen-associated molecular pattern; TLR, toll-like receptor.

McDonald C et al. *Immunology.* 2021;164(4):722-736; García-Merino A. *Cells.* 2021;10(10):2560.

Microglia Polarization in MS: a Simplified View



- In one simplistic formulation, microglia can either trigger neurotoxic pathways leading to neurodegeneration or they can promote neuroprotection, downregulation of inflammation, and repair
  - Intermediate activation states are common
- Neuropathological studies indicate a key role of chronically activated microglia in MS progression
- Evidence suggests that BTK inhibition may favor a shift toward a more protective phenotype

CSF-1R, colony-stimulating factor 1 receptor; CX3CR1, CX3 chemokine receptor 1; NO, nitric oxide; P2X4R, purinergic receptor; ROS, reactive oxygen species; S1PR, S1P receptor; TREM2, triggering receptor expressed on myeloid cells.

Alankus Y et al. *Mult Scler J*. 2018;24:264-264; García-Merino A. *Cells*. 2021;10(10):2560; Voet S et al. *Trends Mol Med.* 2019;25(2):112-123; Zhang D et al. *Molecules*. 2021;26(16):4907.

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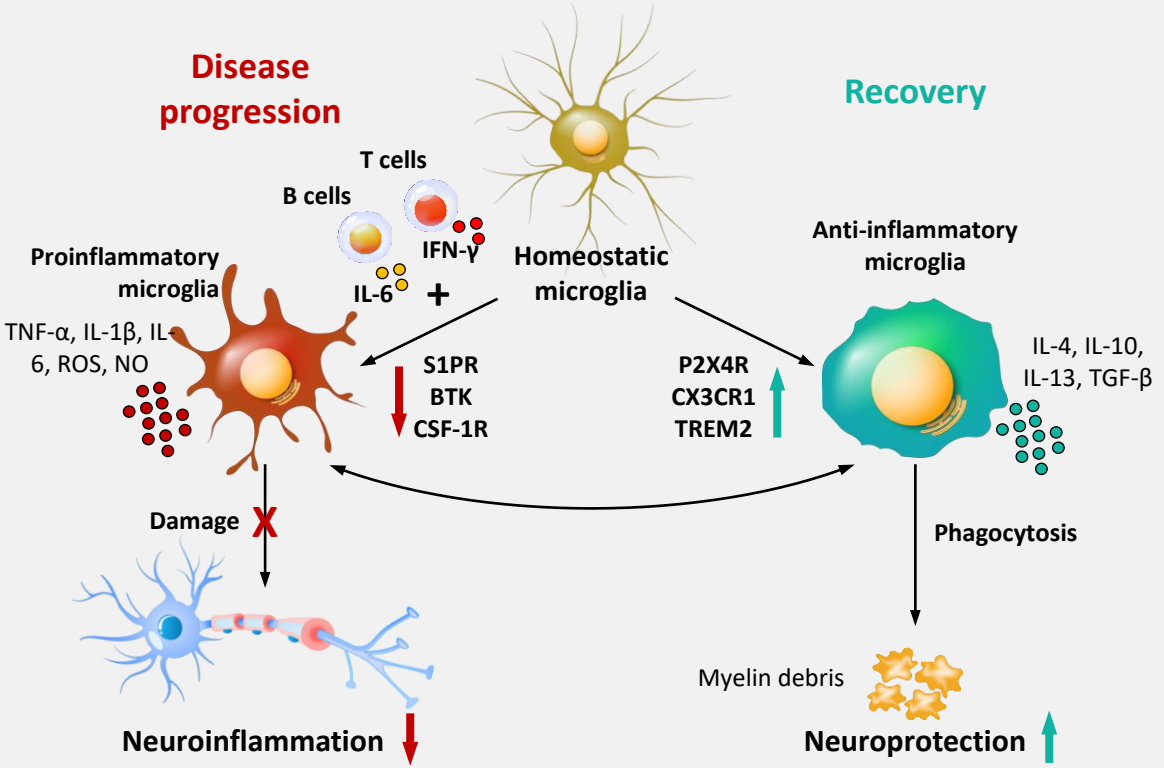

- Microglia can trigger pathways to promote neurodegeneration OR neuroprotection, downregulation of inflammation, and repair (intermediate activation states are common)
- Neuropathological studies indicate a key role of chronically activated microglia in MS progression
- BTK inhibition may favor a shift toward a protective phenotype

CSF-1R, colony-stimulating factor 1 receptor; CX3CR1, CX3 chemokine receptor 1; NO, nitric oxide; P2X4R, purinergic receptor; ROS, reactive oxygen species; S1PR, S1P receptor; TREM2, triggering receptor expressed on myeloid cells.

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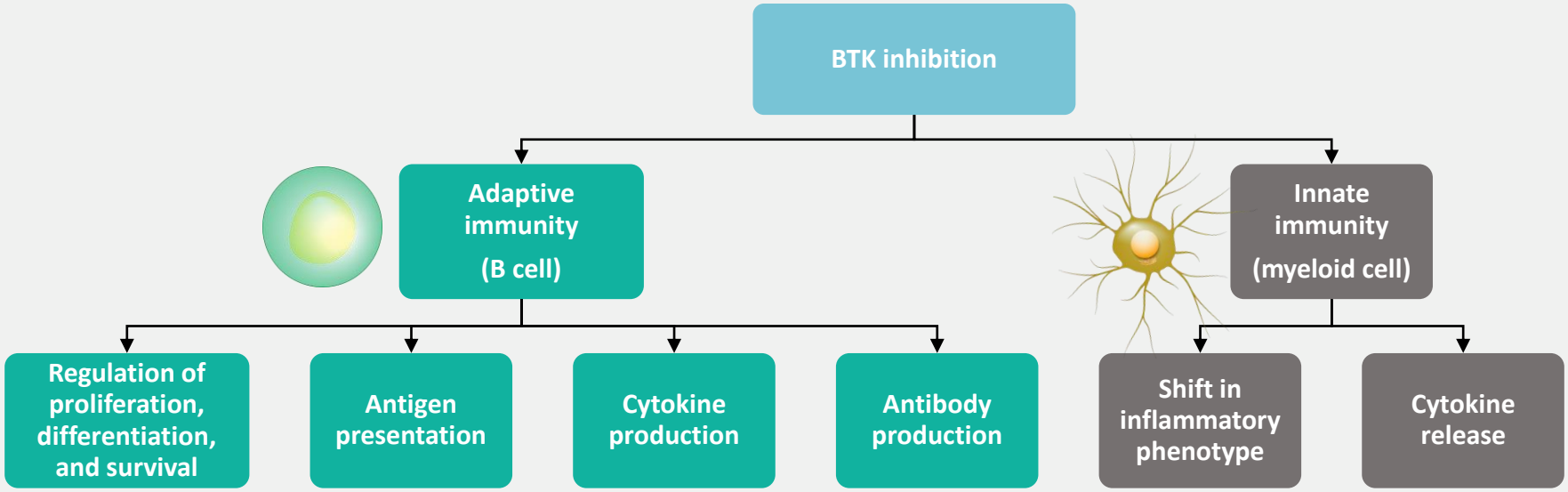
BTK Inhibition in MS: Potential Targeting of Both Adaptive and Innate Immunity



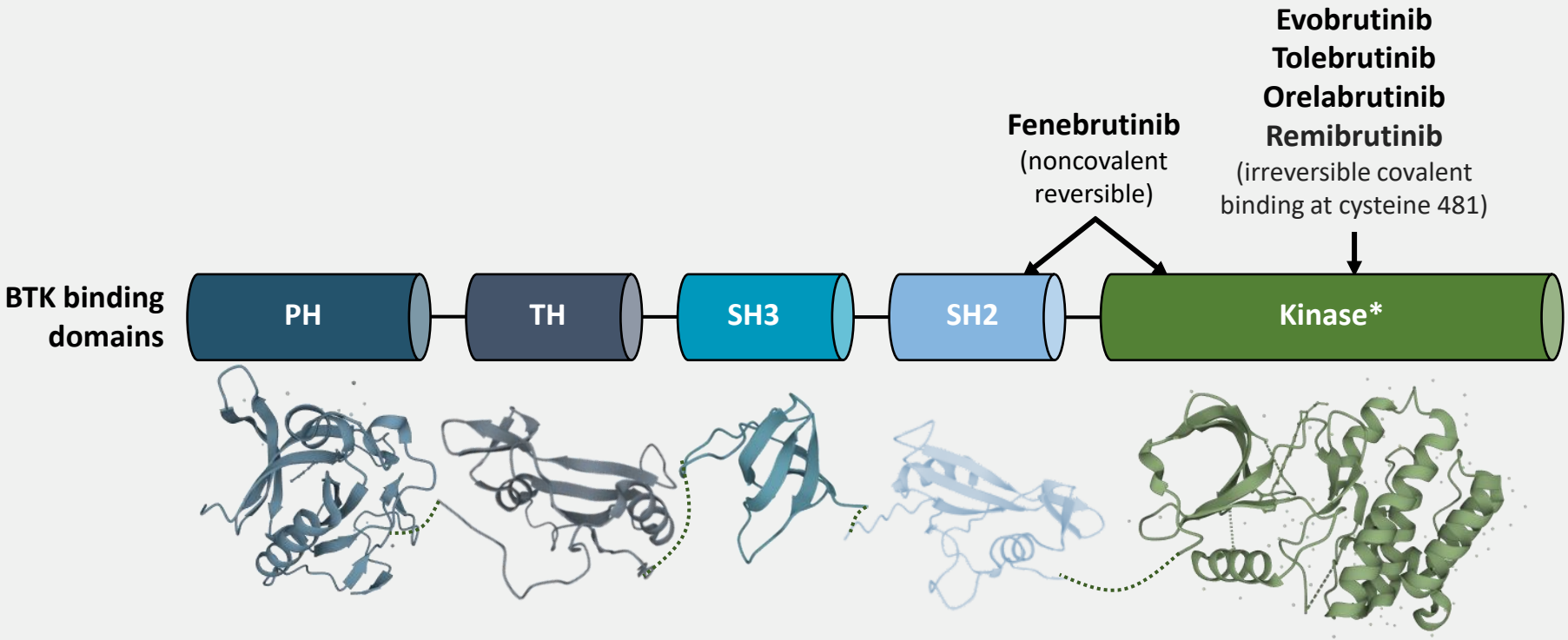
McDonald C et al. *Immunology.* 2021;164(4):722-736.

BTK Inhibitors Currently in Development for MS

BTK inhibition	Patient population	Study phase	Study (projected completion)
Evobrutinib	Relapsing forms of MS	Phase 3	evolutionRMS 1 (2026) evolutionRMS 2 (2026)
Tolebrutinib	Relapsing and progressive forms of MS	Phase 3	GEMINI 1 (2023) GEMINI 2 (2023) HERCULES (2024) PERSEUS (2024)
	Ocrelizumab or rituximab-experienced MS	Phase 2	NCT04742400 (2022)
Fenebrutinib	PPMS and relapsing forms of MS	Phase 3	FENtrepid (2026) FENhance (2025)
		Phase 2	FENopta (2024)
Remibrutinib	Relapsing forms of MS	Phase 3	NCT05147220 (2029)
Orelabrutinib	RRMS	Phase 2	NCT04711148 (2024)

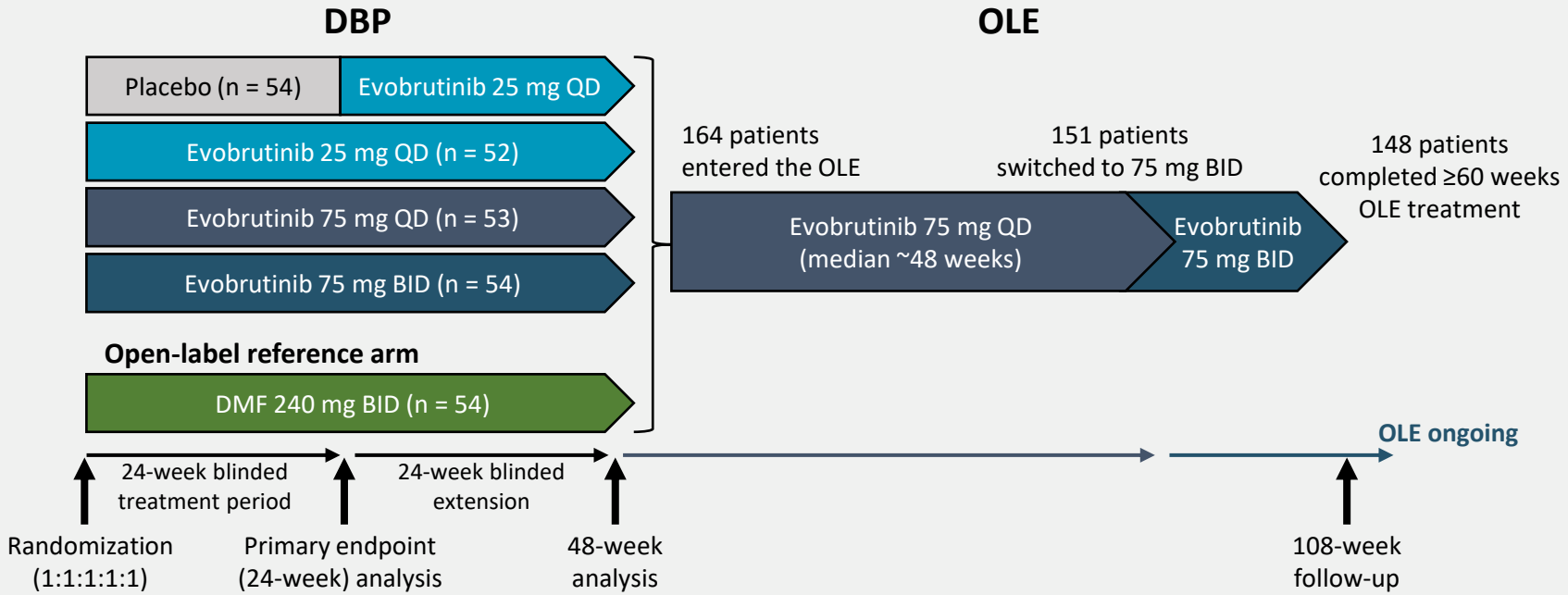
PPMS, primary progressive MS; RRMS, relapsing-remitting MS.
ClinicalTrials.gov. Accessed November 21, 2022. https://clinicaltrials.gov/.

Binding Characteristics of Emerging BTK Inhibitors



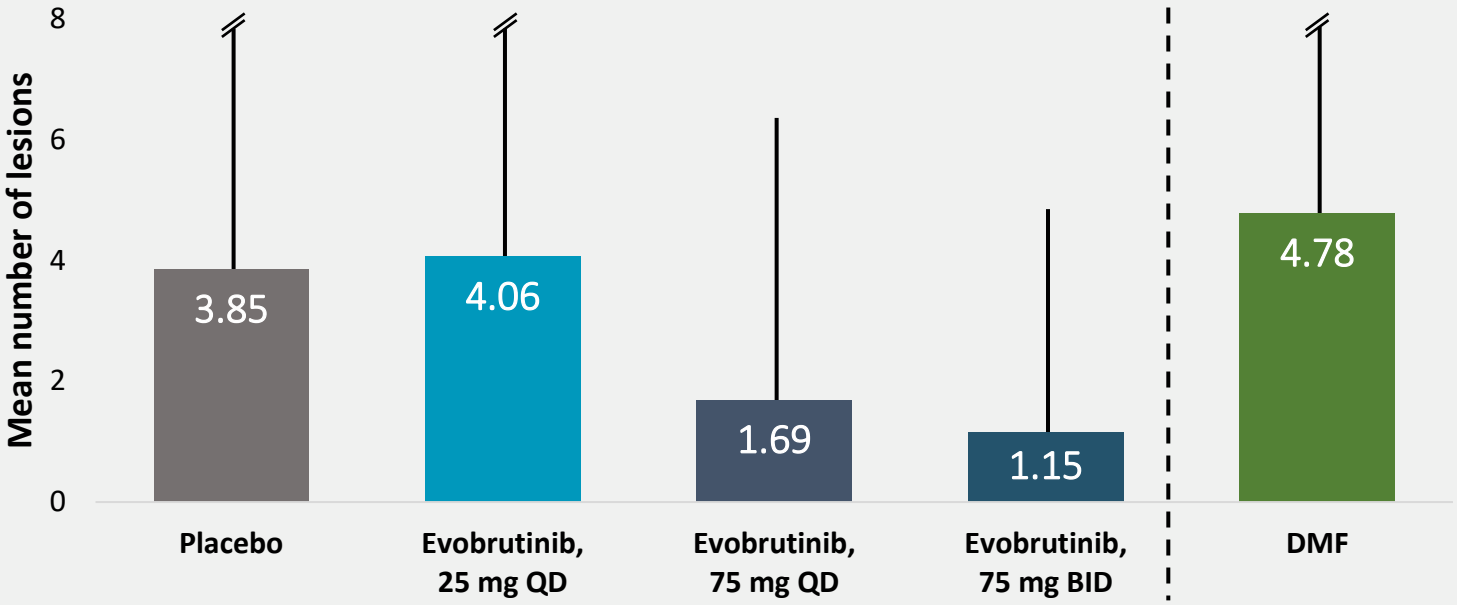
PH, pleckstrin homology; TH, tec homology; SH3 Src homology 3; SH2, Src homology 2.
*Contains the C481 residue (site of irreversible BTK and BTK inhibitor binding) and the Y551 phosphorylation activation site.
McDonald C et al. *Immunology.* 2021;164(4):722-736.

Evobrutinib for the Treatment of Relapsing MS



BID, twice daily; DBP, double-blind period; OLE, open-label extension; QD, once daily.

Impact of Evobrutinib on Number of Gd-Enhancing Lesions Weeks 12-24 in Patients With Relapsing MS



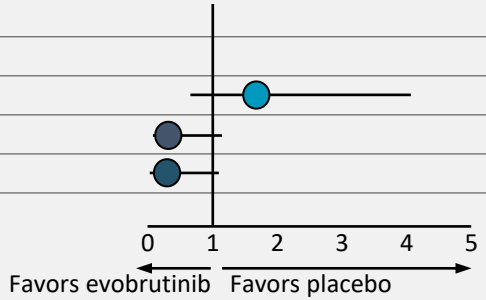
Gd, gadolinium.

Montalban X et al. *N Engl J Med.* 2019;380(25):2406-2417.

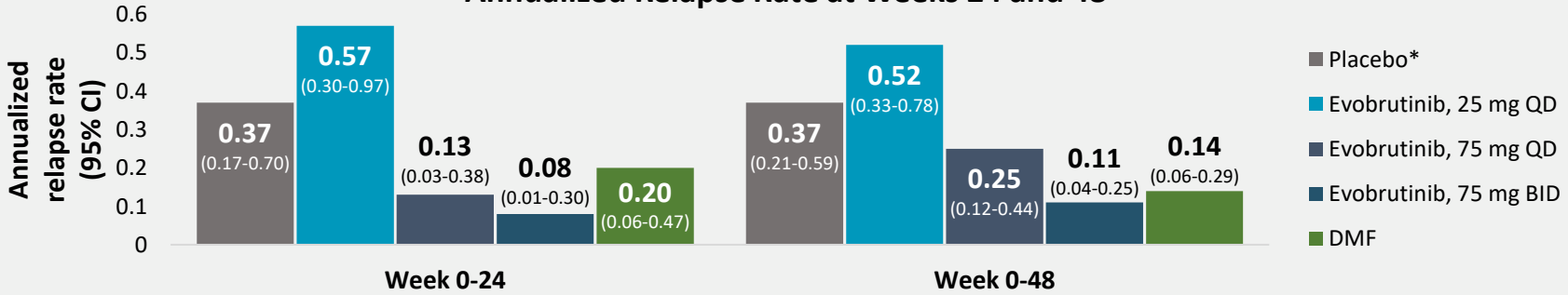
Effects of Evobrutinib Treatment on Measures of Relapse in Patients With MS

Relapse Rate Ratio and Annualized Relapse Rate at Week 24

Trial group	Relapse rate ratio (95% CI)	Annualized relapse rate (95% CI)
Placebo		0.37 (0.17-0.70)
Evobrutinib		
25 mg QD	1.66 (0.67-4.09)	0.57 (0.30-0.97)
75 mg QD	0.31 (0.08-1.20)	0.13 (0.03-0.38)
75 mg BID	0.23 (0.05-1.09)	0.08 (0.01-0.30)
DMF		0.20 (0.06-0.47)



Annualized Relapse Rate at Weeks 24 and 48



*Placebo was administered in the first 24 weeks. At week 24, participants were switched to evobrutinib 25 mg QD.

Montalban X et al. *N Engl J Med.* 2019;380(25):2406-2417.

Evobrutinib Safety and Tolerability

AE	Placebo-evobrutinib 25 mg QD (n = 54)	Evobrutinib, 25 mg QD (n = 52)	Evobrutinib, 75 mg QD (n = 53)	Evobrutinib, 75 mg BID (n = 54)	DMF (n = 54)
Any AE	30 (56)	28 (54)	35 (66)	34 (63)	35 (65)
Any grade 3 or 4 AE	6 (11)	1 (2)	7 (13)	8 (15)	7 (13)
Serious AE	2 (4)	2 (4)	2 (4)	4 (7)	2 (4)
AE leading to discontinuation	5 (9)	3 (6)	6 (11)	7 (13)	2 (4)
AE deemed by investigator to be related to trial agent	14 (26)	10 (19)	15 (28)	18 (33)	26 (48)
Infection	16 (30)	17 (33)	10 (19)	12 (22)	12 (22)
Neoplasm	2 (4)	0	0	0	1 (2)
Most common AEs					
Nausea	0	2 (4)	0	1 (2)	3 (6)
Diarrhea	2 (4)	1 (2)	0	0	4 (7)
Nasopharyngitis	5 (9)	9 (17)	3 (6)	7 (13)	2 (4)
Upper respiratory tract infection	2 (4)	1 (2)	1 (2)	1 (2)	3 (6)
Urinary tract infection	5 (9)	2 (4)	1 (2)	0	2 (4)
Increase in alanine aminotransferase	4 (7)	3 (6)	6 (11)	5 (9)	3 (6)
Increase in aspartate aminotransferase	1 (2)	1 (2)	2 (4)	4 (7)	2 (4)
Increase in lipase	5 (9)	2 (4)	5 (9)	5 (9)	3 (6)
Increase in creatinine	1 (2)	0	3 (6)	3 (6)	1 (2)
Low lymphocyte count	0	0	0	1 (2)	5 (9)
Arthralgia	1 (2)	2 (4)	3 (6)	0	4 (7)
Headache	2 (4)	3 (6)	2 (4)	1 (2)	1 (2)
Flushing	0	0	0	0	12 (22)

AE, adverse event.

Montalban X et al. *N Engl J Med.* 2019;380(25):2406-2417.

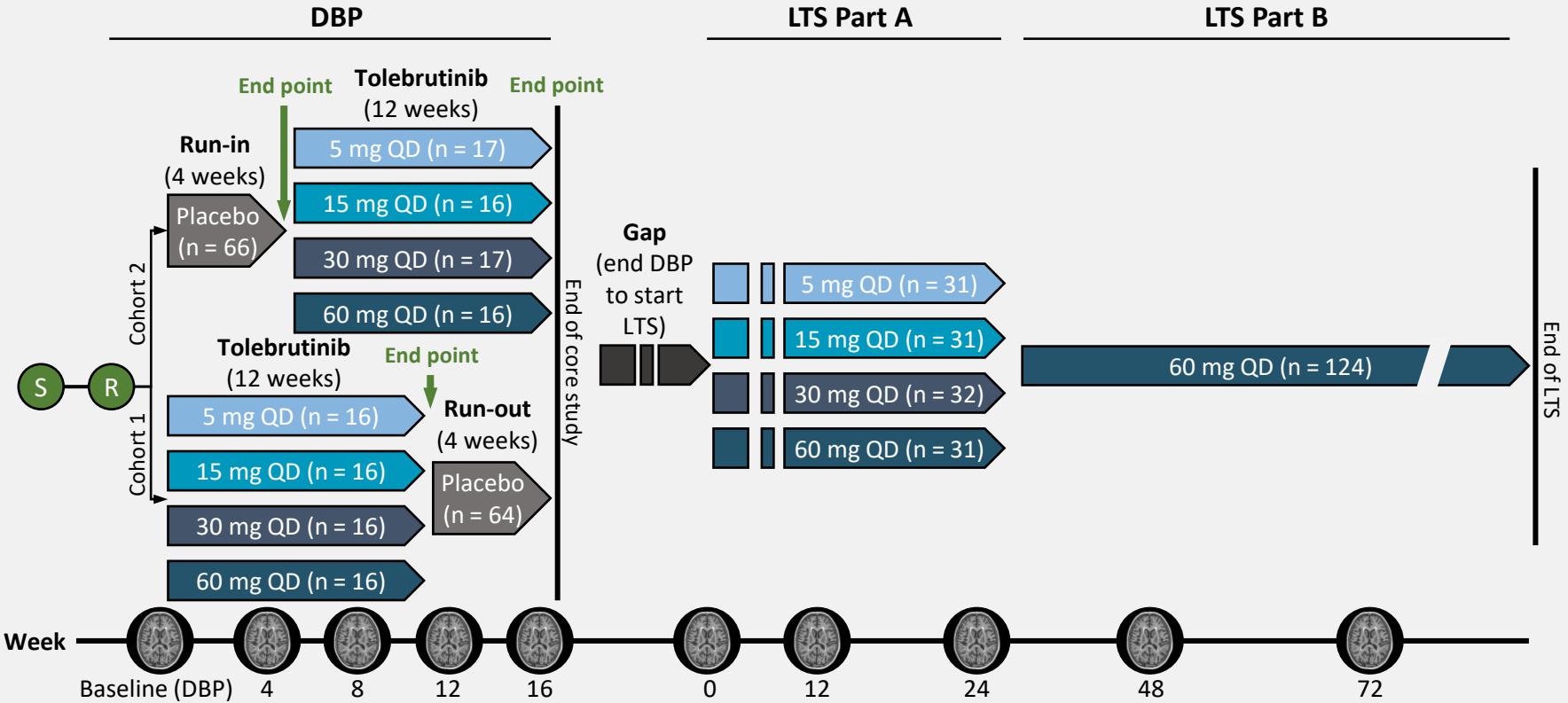
Long-Term Safety of Evobrutinib: OLE Findings

- Safety profile similar to that observed during the DBP
  - Most TEAEs were mild or moderate, and no new safety concerns were observed
  - Common TEAEs (≥5%) were balanced across treatment groups during the DBP
  - Transient treatment-related liver aminotransferase elevations were not observed in the OLE after prolonged treatment or after switch to evobrutinib 75 mg BID
  - Evobrutinib 75 mg BID was not associated with an increased incidence of infections
- IgG, IgA, and IgM levels were WNL through OLE week 48 in the majority of patients
- Changes in immune cells and Ig levels over 96 weeks were not associated with enhanced infection risk
- Long-term evobrutinib treatment was generally well tolerated

TEAE, treatment-emergent AE; WNL, within normal limits.

Montalban X, Arnold DL. Presented at the European Charcot Foundation 28th Annual Meeting: Virtual Meeting; 2020;
Montalban X et al. *Neurology.* 2022;98(18 supplement):2812.

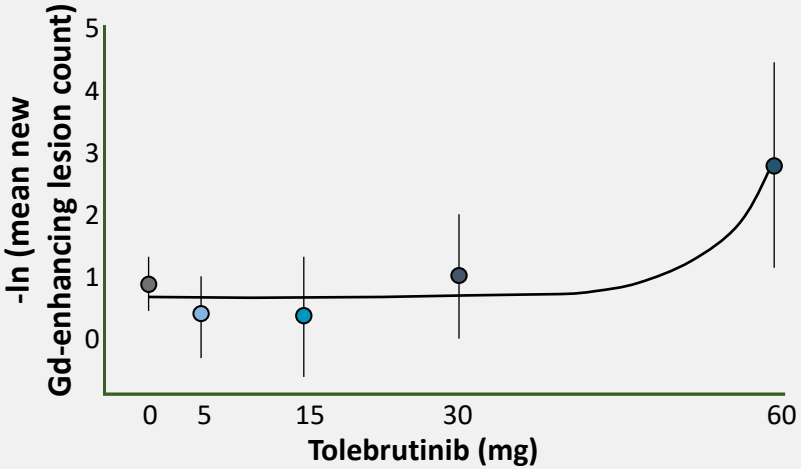
Tolebrutinib for the Treatment of Relapsing MS

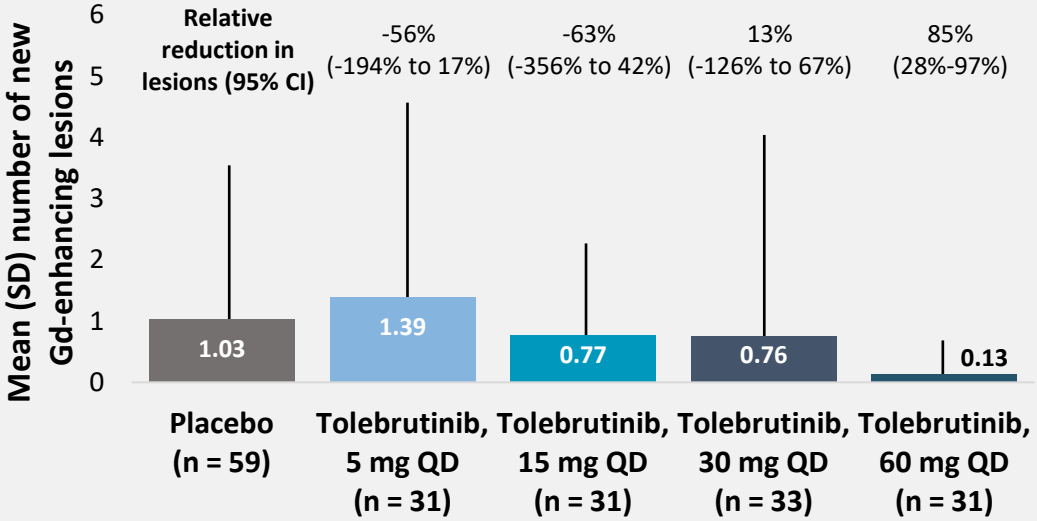


LTS, long-term safety; R, randomization; S, screening.

Reich DS et al. *Lancet Neurol.* 2021;20(9):729-738.

New Gd-Enhancing Lesions After 12 Weeks of Tolebrutinib Treatment

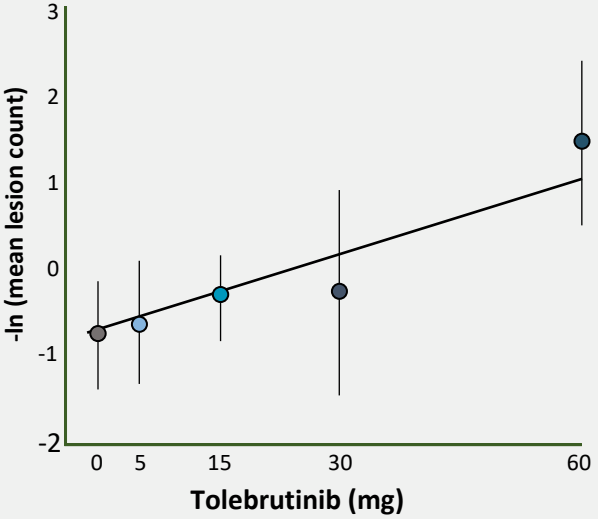




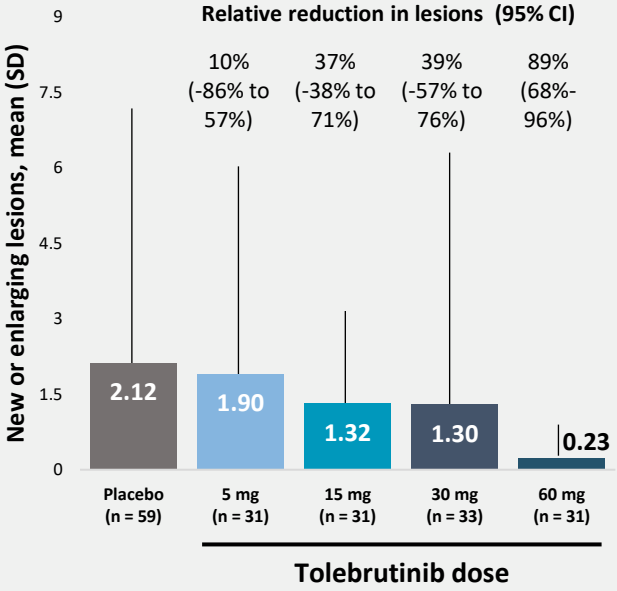
Reich DS et al. *Lancet Neurol.* 2021;20(9):729-738.

New or Enlarging T2 Lesions and Gd-enhancing Lesions After 12 Weeks of Tolebrutinib Treatment

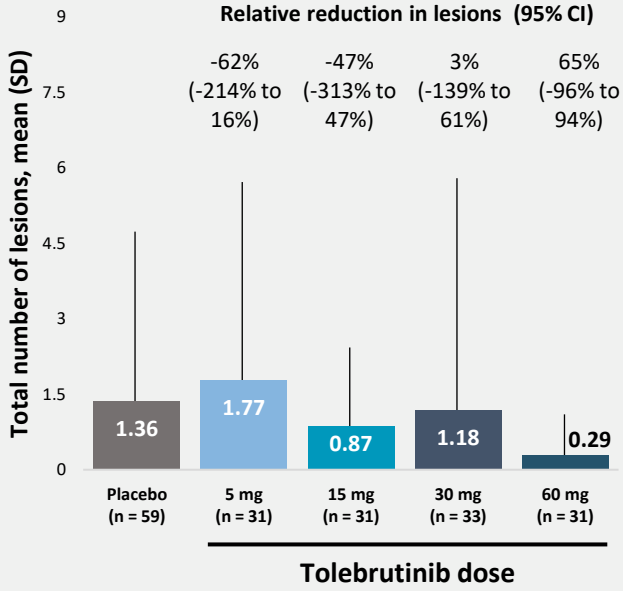
Estimated Dose-Response Curve for the Number of New or Enlarging T2 Lesions



Mean (SD) Number of New or Enlarging T2 Lesions



Mean (SD) Total Number of Gd-Enhancing Lesions



Reich DS et al. *Lancet Neurol.* 2021;20(9):729-738.

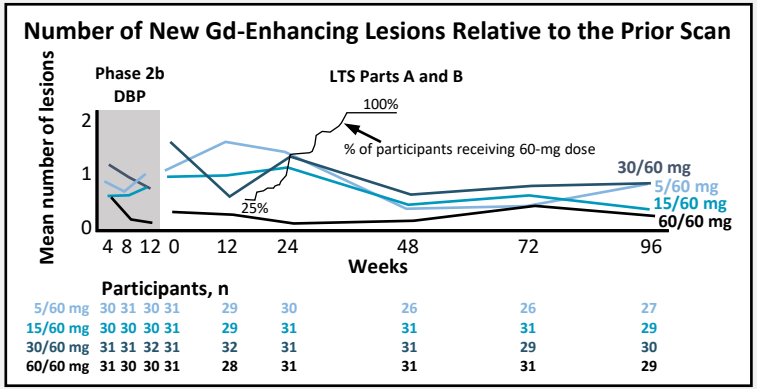
Tolebrutinib Safety and Tolerability

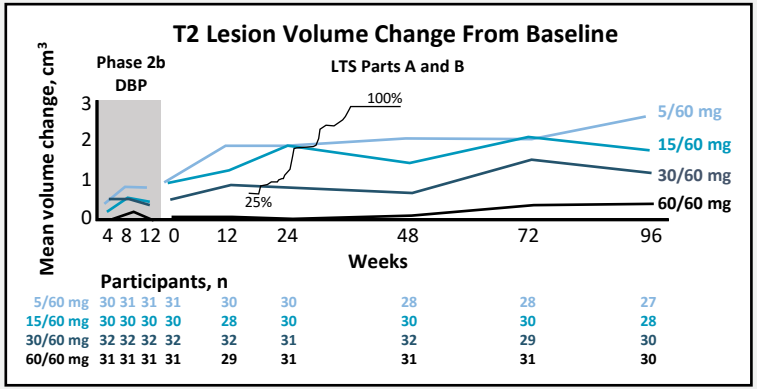
	All participants (n = 130)	Tolebrutinib, 5 mg (n = 33)	Tolebrutinib, 15 mg (n = 32)	Tolebrutinib, 30 mg (n = 33)	Tolebrutinib, 60 mg (n = 32)
Participants with ≥1 AE					
Any AE	70 (54)	19 (58)	17 (53)	18 (55)	16 (50)
Severe AEs	1 (1)	0	0	0	1 (3)
Serious AEs	1 (1)	0	0	0	1 (3)
AEs leading to death	0	0	0	0	0
AEs leading to study discontinuation	0	0	0	0	0
Any AE leading to study treatment discontinuation	0	0	0	0	0
Any treatment-related AE	17 (13)	5 (15)	1 (3)	4 (12)	7 (22)
AEs occurring in >2 participants during 12 weeks of tolebrutinib treatment					
Headache	9 (7)	1 (3)	3 (9)	1 (3)	4 (13)
Upper respiratory tract infection	6 (5)	2 (6)	2 (6)	1 (3)	1 (3)
Nasopharyngitis	5 (4)	1 (3)	0	1 (3)	3 (9)
Back pain	4 (3)	1 (3)	1 (3)	2 (6)	0
Peripheral oedema	4 (3)	2 (6)	0	0	2 (6)
Accidental overdose	3 (2)	0	0	0	3 (9)
Gastroenteritis	3 (2)	1 (3)	0	0	2 (6)
Alanine aminotransferase increased	3 (2)	1 (3)	0	1 (3)	1 (3)
Respiratory tract infection	3 (2)	0	1 (3)	1 (3)	1 (3)
Muscle spasticity	3 (2)	0	0	1 (3)	2 (6)
Oropharyngeal pain	3 (2)	1 (3)	0	1 (3)	1 (3)
Alopecia	3 (2)	1 (3)	1 (3)	0	1 (3)

Reich DS et al. *Lancet Neurol.* 2021;20(9):729-738.

Long-term Safety and Efficacy of Tolebrutinib

- **Clinical measures**
  - Annualized relapse rate remained low in the 60-mg tolebrutinib group, with ~85% of patients free of relapses at week 72
  - EDSS scores also remained stable at week 72
- **Radiographic findings**
  - New Gd-enhancing lesion counts remained low for the tolebrutinib 60/60-mg arm through week 96 and were reduced in lower dose arms weeks 48 through 96
  - T2 lesion volume change remained low in the 60/60-mg arm
- **Safety and tolerability**
  - Tolerability profile remained favorable
  - No new safety signals observed

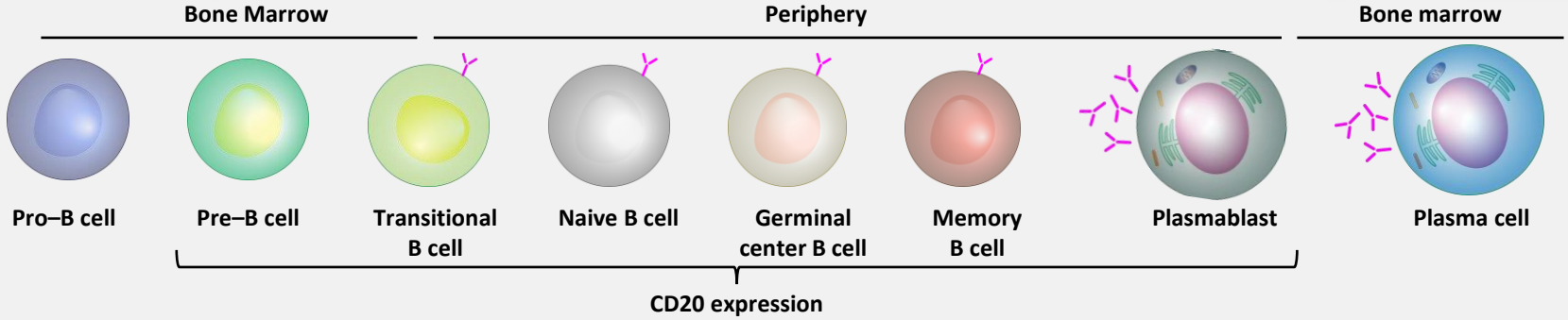




EDSS, Expanded Disability Status Scale.

Reich DS et al. Presented at ECTRIMS: Amsterdam, Netherlands; 2022; Oh J et al. Presented at ACTRIMS Forum: West Palm Beach, FL; 2022.

B-Cell Depletion vs B-Cell Modulation: Potential Clinical Implications

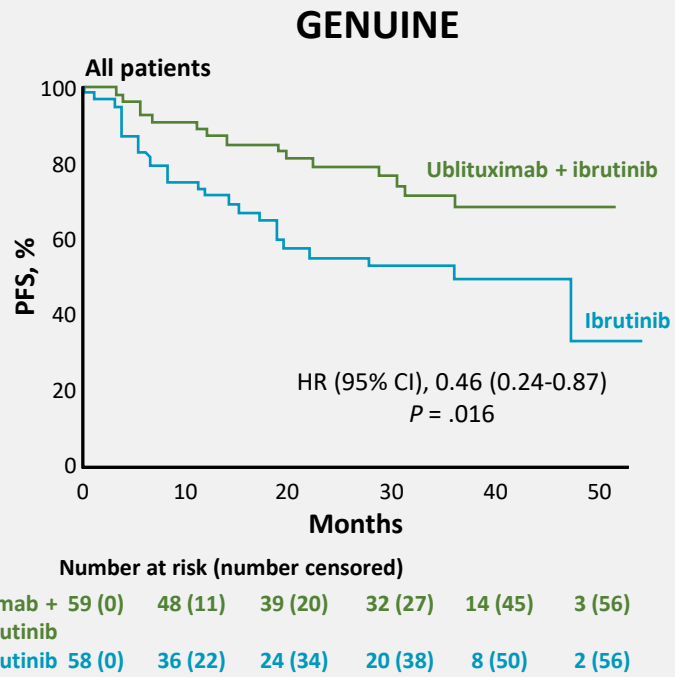


- Current anti-CD20 therapies (ie, rituximab, ofatumumab, ocrelizumab) induce **cell lysis and depletion of the B-cell population** whereas BTK inhibitors **modulate B-cell activity**
- Modulation of activity has the potential to circumvent issues related to chronic B-cell depletion (eg, humoral deficiency)
- Differing mechanisms of action raise the possibility of combining therapies to achieve increased efficacy

Musette P, Bouaziz JD. *Front Immunol.* 2018;9:622; García-Merino A. *Cells.* 2021;10(10):2560.

Combining Anti-CD20 and BTK Inhibitor Therapy: Data From CLL Studies

Study	Patients	Treatment groups	Study findings (combined vs monotherapy)
Burger et al, 2019	Relapsed and treatment-naive high-risk CLL	Ibrutinib vs rituximab + ibrutinib	• No improvement in PFS • Faster achievement of remission • Lower residual disease • Similar safety
Sharman et al, 2021 (GENUINE)	Relapsed or refractory high-risk CLL	Ibrutinib vs ublituximab + ibrutinib	• Improved PFS (figure) • Similar safety

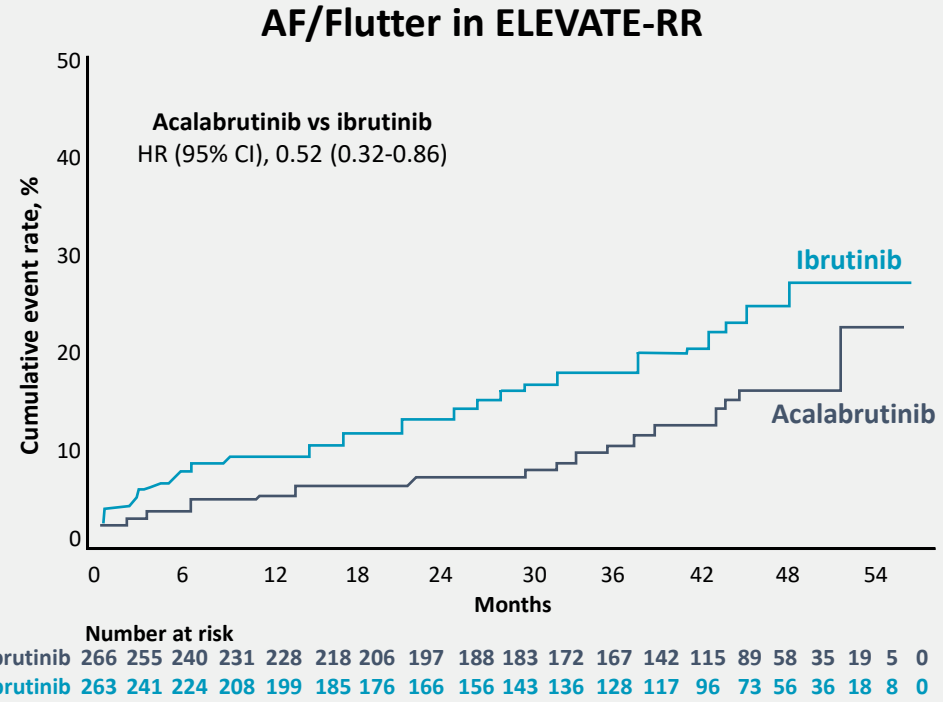


CLL, chronic lymphocytic leukemia; PFS, progression-free survival.

Burger JA et al. *Blood*. 2019;133(10):1011-1019; Sharman JP et al. *Lancet Haematol*. 2021;8(4):e254-e266.

Improved Safety With Second-Generation BTK Inhibitors in the Treatment of CLL

- First-generation BTK inhibitors have been associated with AEs related to off-target inhibition of other tyrosine kinases (eg, EGFR, ITK, and JAK3)
- In ELEVATE-RR, the second-generation BTK inhibitor acalabrutinib was noninferior to the first-generation ibrutinib in efficacy (PFS) and exhibited an improved safety profile
- **Acalabrutinib was associated with fewer AEs, including a significantly lower incidence of cardiac events (eg, AF, hypertension)**



AF, atrial fibrillation; EGFR, epidermal growth factor receptor; ITK, IL-2–inducible T-cell kinase; JAK3, Janus kinase 3.

Byrd JC et al. Presented at the ASCO Annual Meeting: Virtual Meeting; 2021.

Key Points

- Chronic neuroinflammation, driven in part by B lymphocytes and activated microglia, is a key contributor to disability accumulation in relapsing and progressive MS
- Bruton's tyrosine kinase (BTK) plays a central signaling role in the activity of B lymphocytes and myeloid cells, and thus its inhibition has emerged as an important future therapeutic strategy in MS
- A number of BTK inhibitors (including evobrutinib and tolebrutinib, for which phase 2 data have been published) are currently in late-stage development for relapsing MS. These have demonstrated good safety and efficacy with regard to disease activity, disability accumulation, and lesion number and volume
- Two BTK inhibitors, tolebrutinib and fenebrutinib, are currently in late-stage development for progressive MS