Introduction to BTK-Inhibitors

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Disclosures

- Jenny Feng has served on advisory boards for Novartis, Bristol Myers Squibb, TG Therapeutics, Horizon

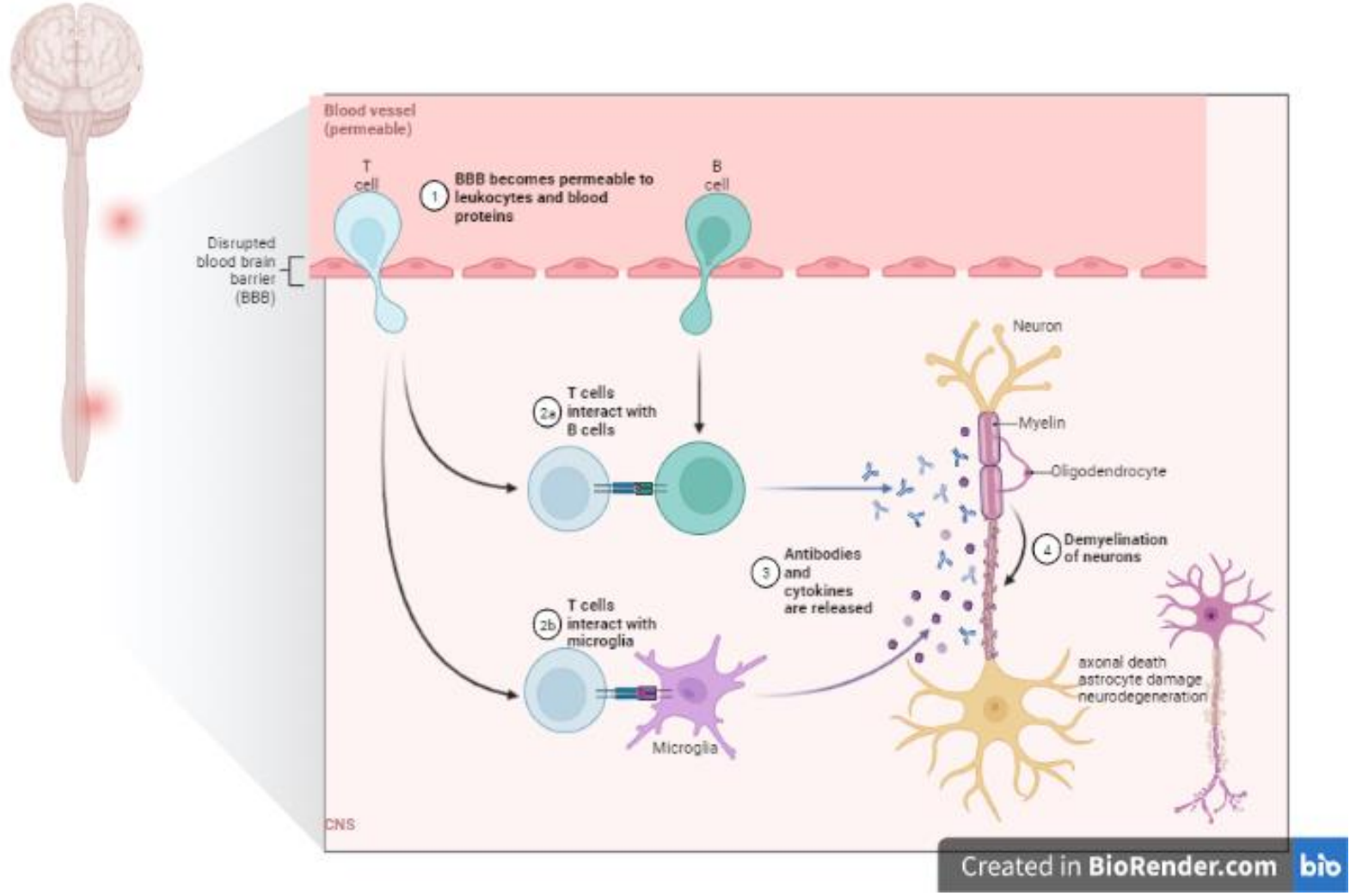
Outline

- Introduction
- What are BTK inhibitors
- Comparison to anti-CD20 therapies
- Review of current clinical trial data
- Clinical considerations
- Conclusion

Current understanding of Multiple Sclerosis Pathophysiology

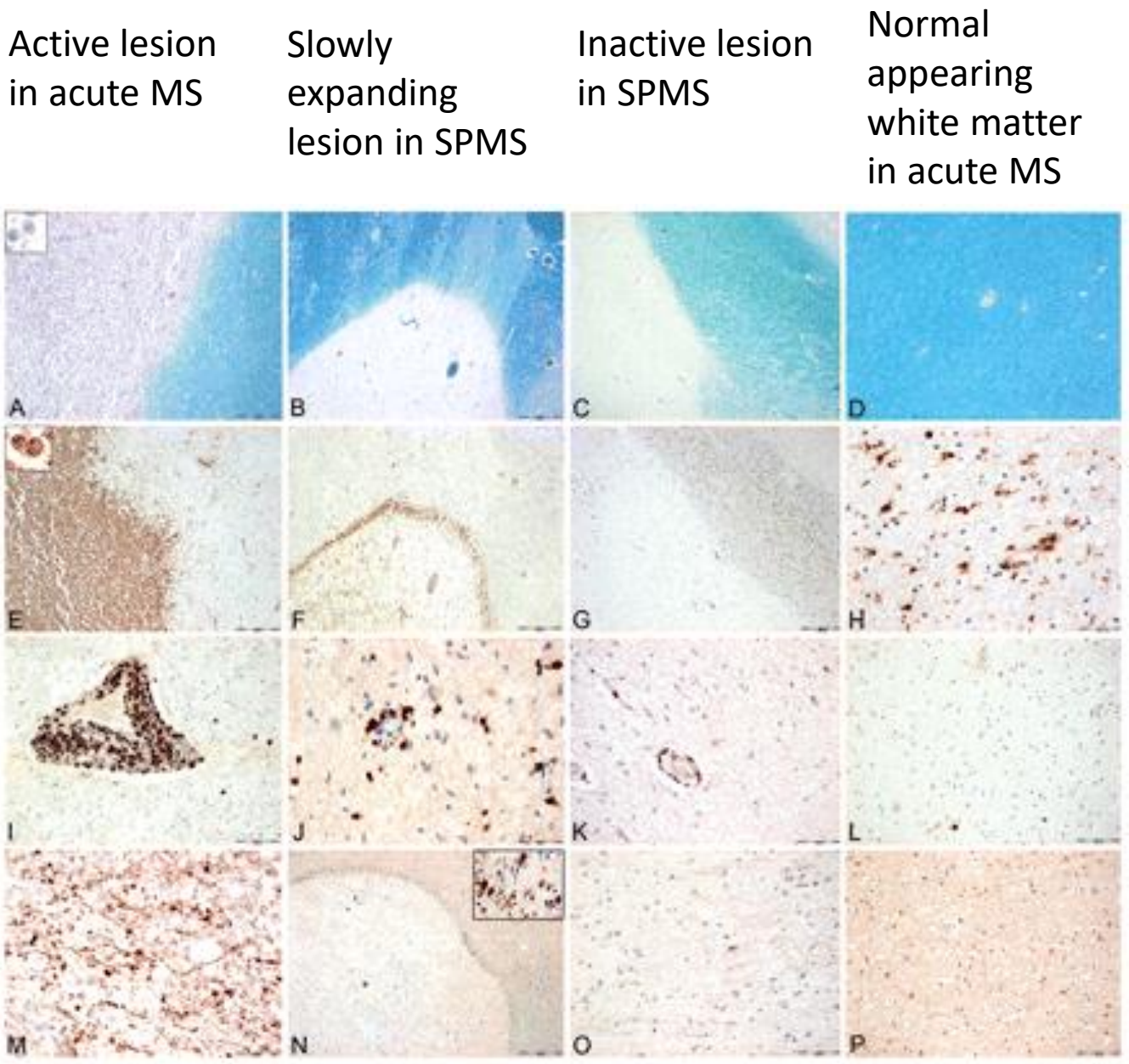
Immune dysregulation in MS

- Autoreactive T-cells in response to specific CNS antigens
- B cells activation → polarize autoreactive T-cells
- Lymphocyte cross blood-brain-barrier → secret proinflammatory cytokines and antibodies → activated macrophages, microglia → damage to myelin, axon, oligodendrocyte, astroglia
- Compartmentalized inflammation → drives progression of disease, cortical demyelination, resistance to DMTs



MS Pathophysiology

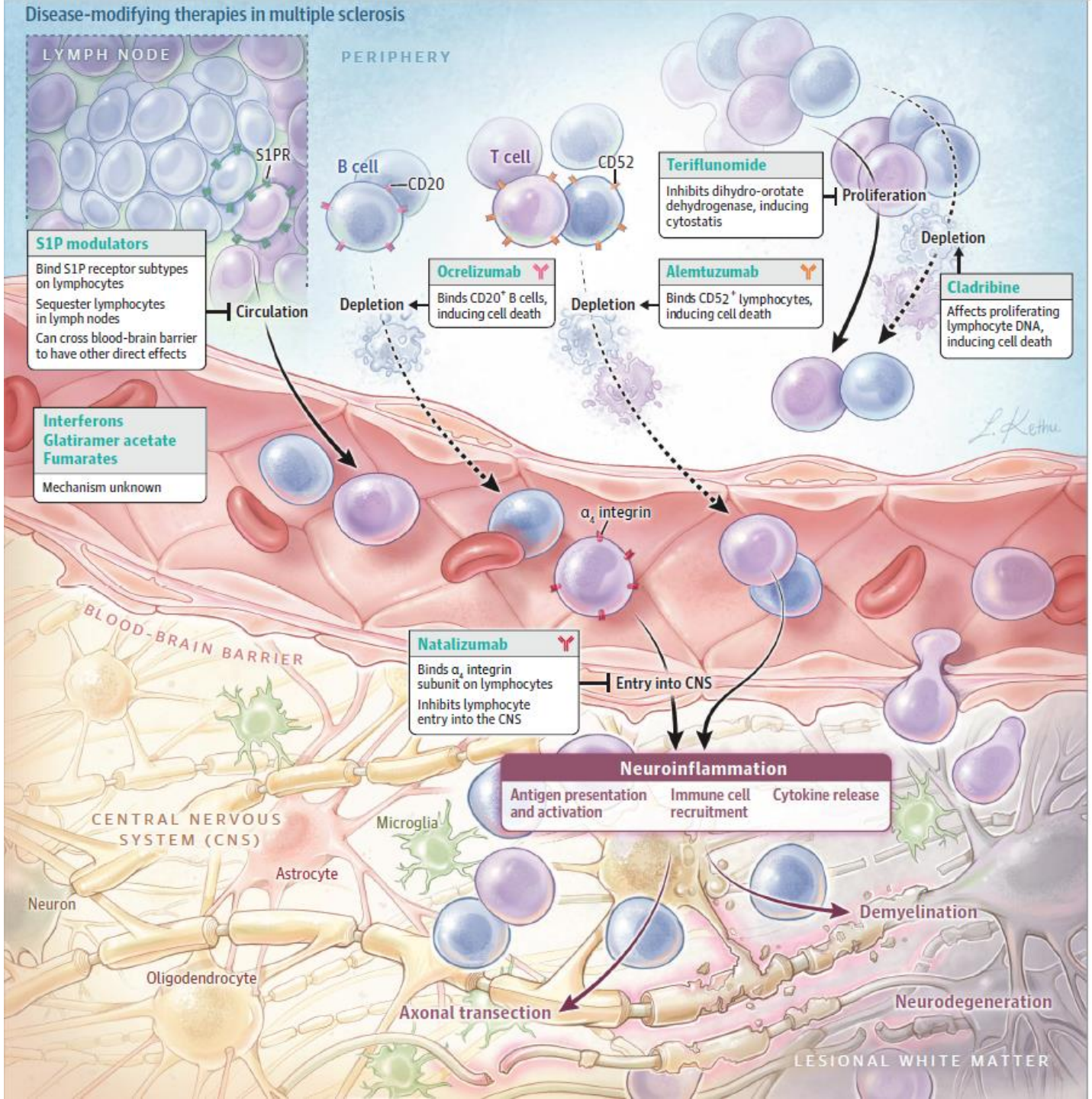
- Heterogeneity in lesion pathology
- Active lesions: predominant lymphocytic inflammation
- Chronic lesions: inactive core with rim of macrophages and microglia, axonal injury, myelin degradation



Frischer et al. Brain. 2009;132(5):1175-1189.

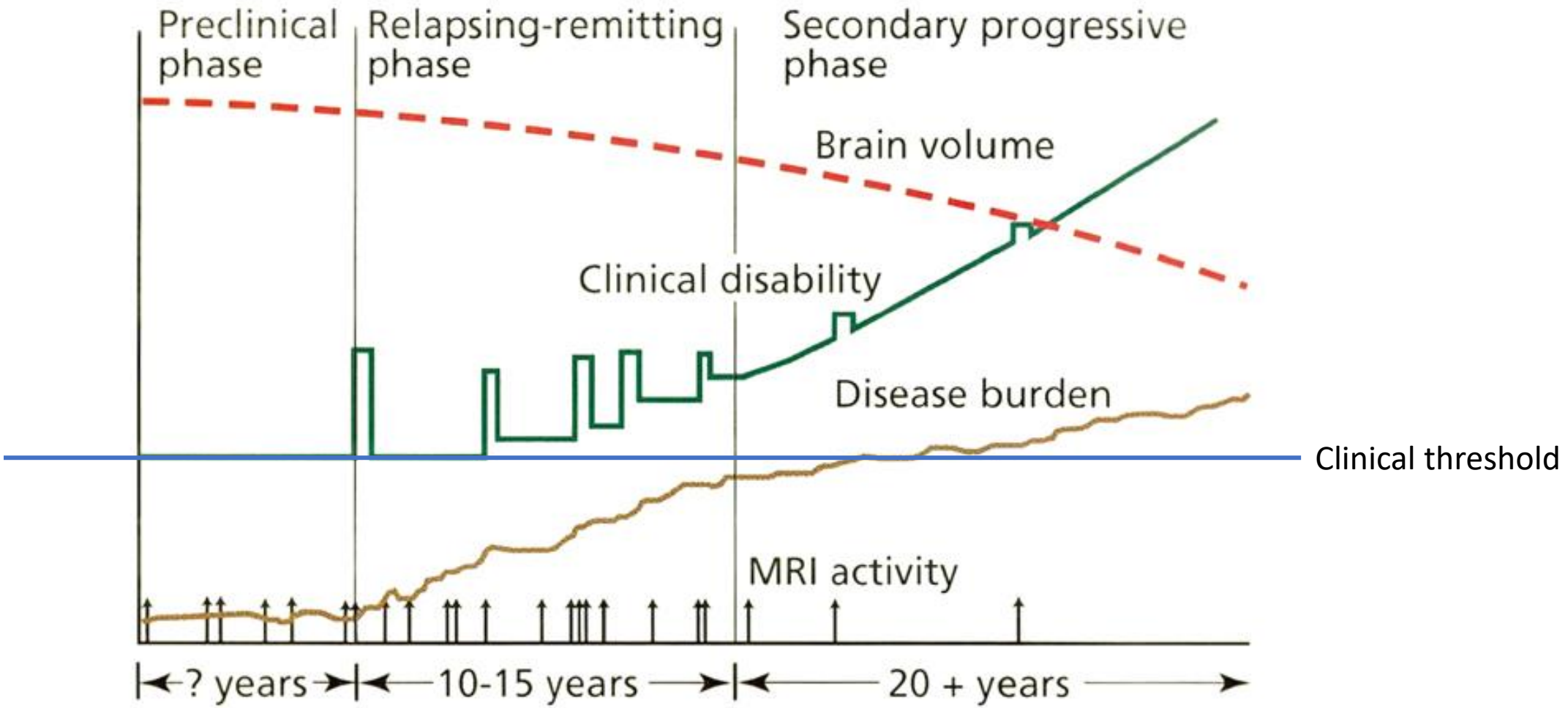
Current FDA-approved MS Therapies

Year approved	DMT	MOA	Route of administration
1993	Betaseron (interferon beta-1b)	Immunomodulation	Injectable
1996	Avonex (interferon beta-1a)	Immunomodulation	Injectable
	Copaxone (glatiramer acetate)	Immunomodulation	Injectable
1998	Rebif (interferon beta-1a)	Immunomodulation	Injectable
2000	Novantrone (mitoxantrone)	Inhibit cellular replication	Infused
2004	Tysabri (natalizumab)	Altered cell trafficking	Infused
2009	Extavia (interferon beta-1b)	Immunomodulation	Injectable
2010	Gilenya (fingolimod)	Altered cell trafficking	Oral
2012	Aubagio (teriflunomide)	Inhibit cellular replication	Oral
2013	Tecfidera (dimethyl fumarate)	Immunomodulation	Oral
2014	Plegridy (peg-interferon beta-1a)	Immunomodulation	Oral
	Lemtrada (alemtuzumab)	Anti-CD52 antibody	Infused
2015	Glatopa (glatiramer acetate)	Immunomodulation	Injectable
2017	Ocrevus (ocrelizumab)	Anti-CD20 antibody	Infused
2019	Vumerity (diroximel fumarate)	Immunomodulation	Oral
	Mayzent (siponimod)	Altered cell trafficking	Oral
	Mavenclad (cladribine)	Inhibit cellular replication	Oral
2020	Kesimpta (ofatumumab)	Anti-CD20 antibody	Injectable
	Bafiertam (monomethyl fumarate)	Immunomodulation	Oral
	Zeposia (ozanimod)	Altered cell trafficking	Oral
2021	Ponvory (ponesimod)	Altered cell trafficking	Oral
2023	Briumvi (ublituximab)	Anti-CD20 antibody	Infused



McGinley et al. JAMA 2021

MS Disease Course



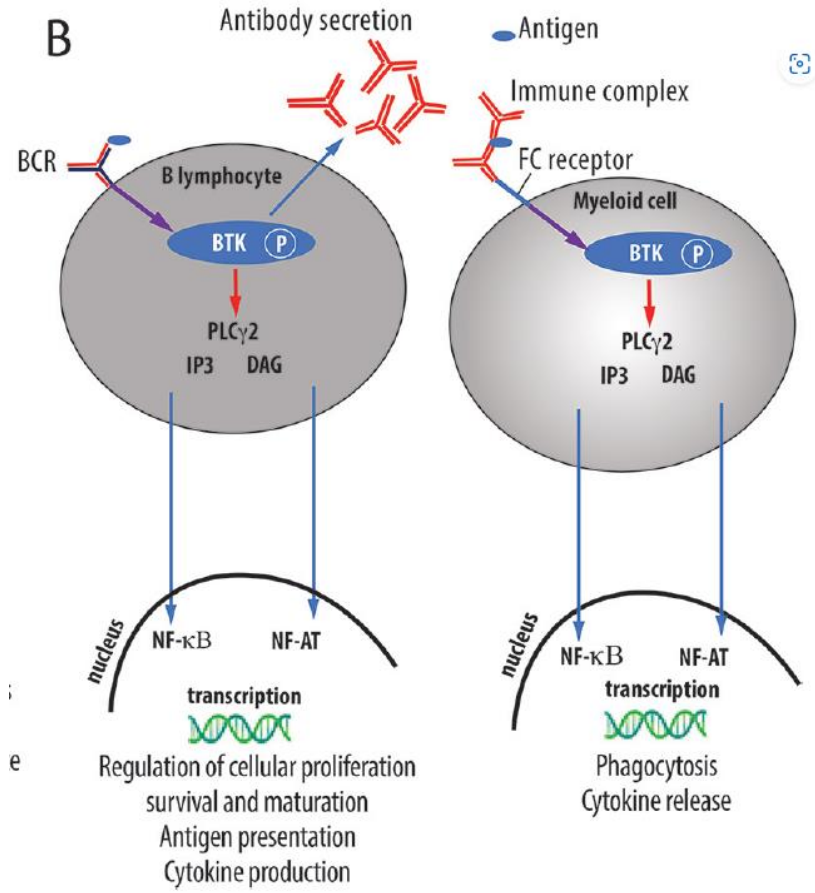
Hersh et al, Cleveland Clinic CME, 2018

BTK-Inhibitors

BTK

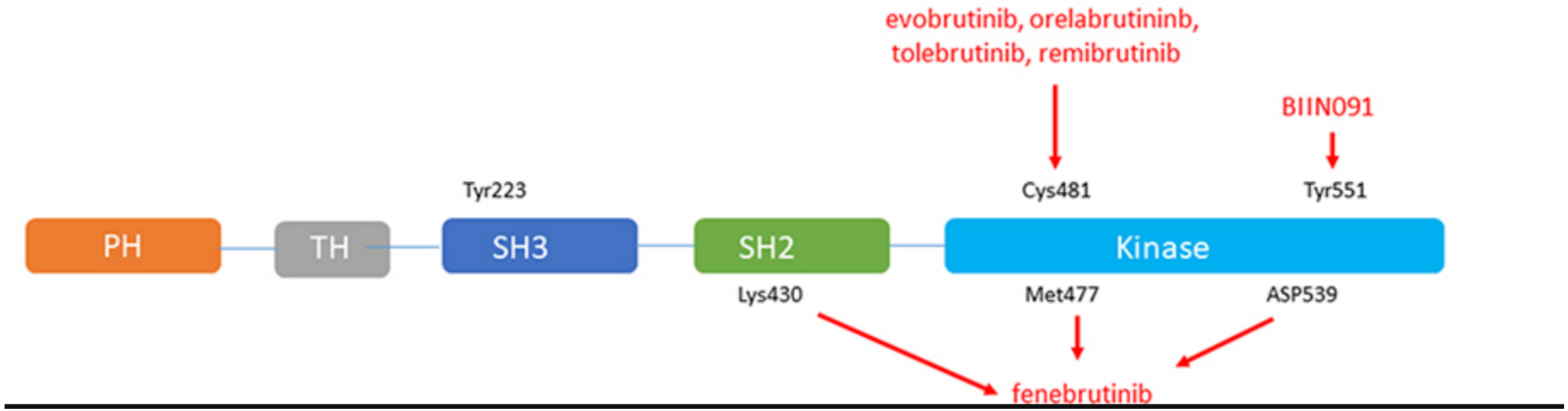
- Bruton tyrosine kinase (BTK)
  - BTK gene discovered in early 1990s
  - Tec family of non-receptor, cytoplasmic protein tyrosine kinases
  - Expressed in hematological cells
  - Crucial for B-cell development and maturation
- BTK participates in B-cell and myeloid cell (microglia, macrophages, monocytes) signaling pathways
  - Controls progression of B-cell and myeloid cell maturation, differentiation, activation, survival
  - Controls cytokine release, reactive oxygen species production, inflammasome activation

Ogden Carr Bruton



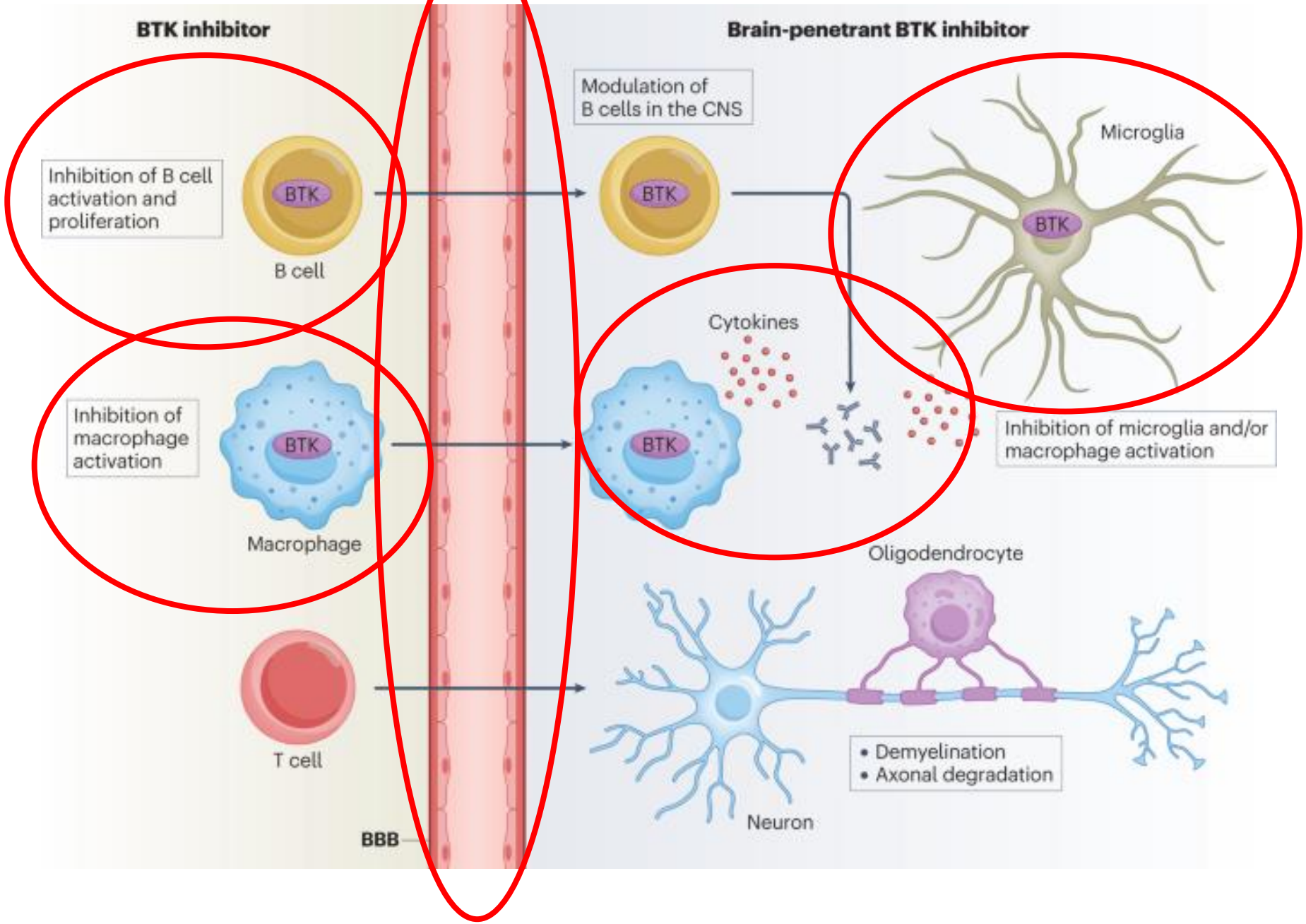
Kramer et al. Nat Rev Neurol. Apr 2023; Jayagopal et al. Practical Neurology Feb 2022

BTK Inhibitors



- BTK inhibitors initially developed for treatment of B-cell malignancies
  - Ibrutinib (2007), 1st selective BTK-i
- Being developed for treatment of a variety of autoimmune diseases
- Small, lipophilic, crosses BBB → reduce compartmentalized inflammation in CNS
- Preserves B-cell viability and survival

Kramer et al. Nat Rev Neurol. Apr 2023; Jayagopal et al. Practical Neurology Feb 2022



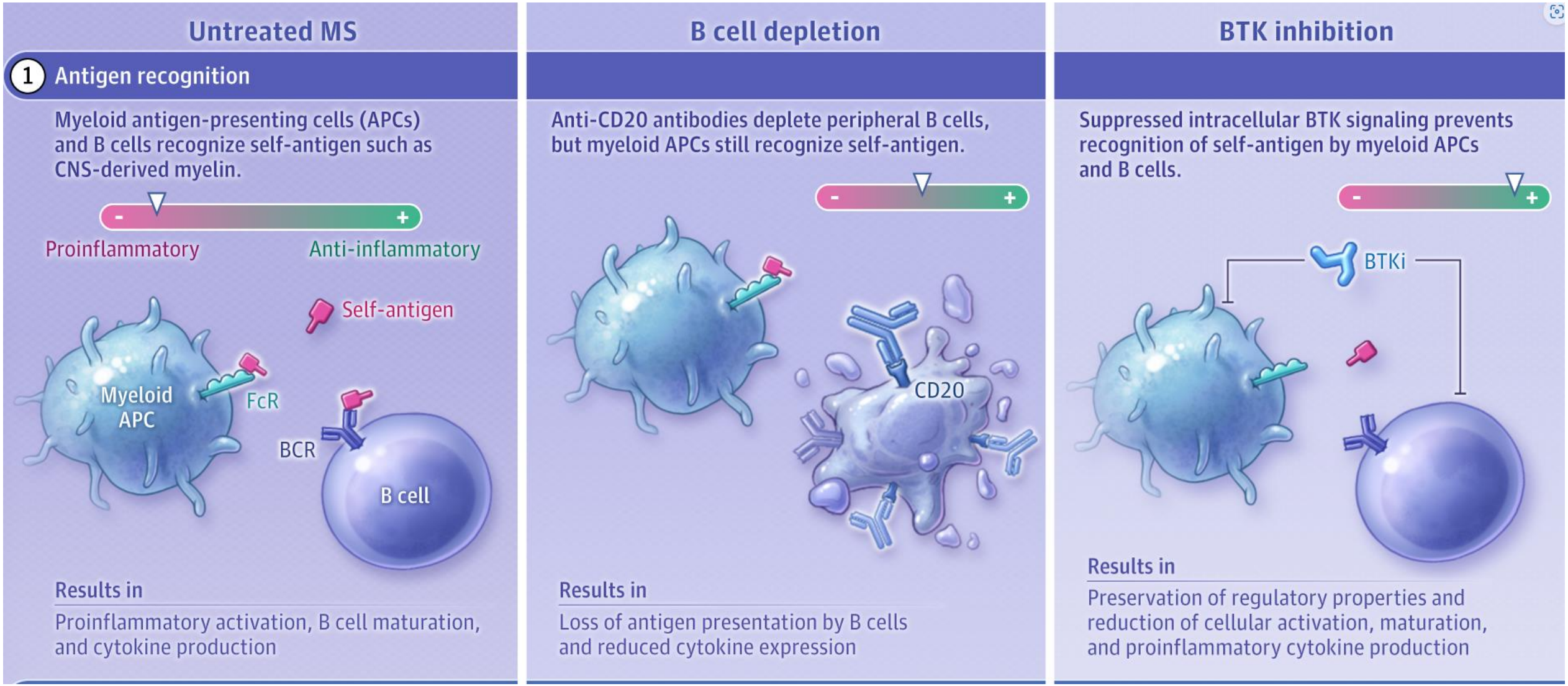
Kramer et al. Nat Rev Neurol. Apr 2023

BTK Inhibitors in MS

BTKi	Chemical bond	Inhibition site	Selectivity
Evobrutinib	Covalent, irreversible	Kinase domain C481 residue	Selective
Tolebrutinib	Covalent, irreversible	Kinase domain C481 residue	Binds other kinases
Fenebrutinib	Noncovalent, reversible	SH2 domain K430 residue, kinase domain M477 and D539 residues	Binds other kinases
Remibrutinib	Covalent, irreversible	Kinase domain C481 residue	Highly selective
Orelabrutinib	Covalent, irreversible	Kinase domain C481 residue	Highly selective
BIIB091	Noncovalent, reversible	Tyr551 Domain	Highly selective

Comparison to B-cell depleters

Differences compared to anti-CD mAbs



Dybowski et al. JAMA Neurol. 2023

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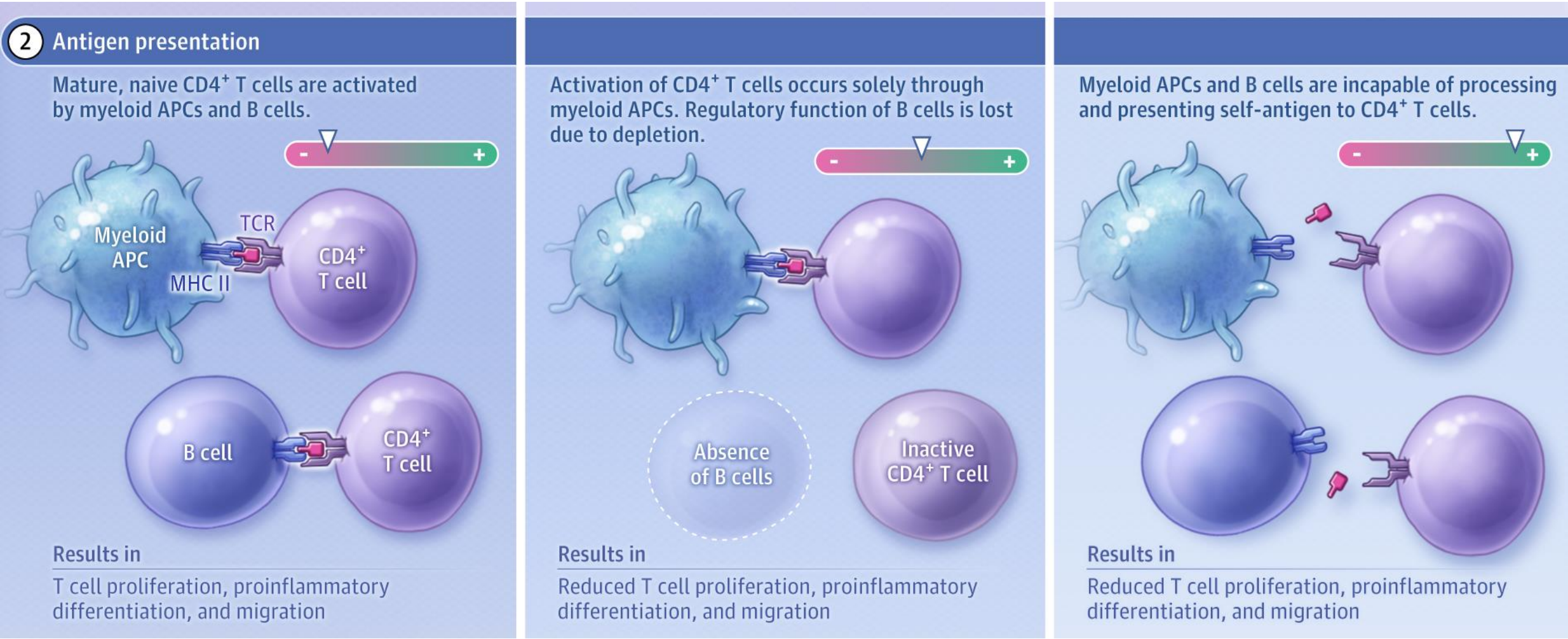

Dybowski et al. JAMA Neurol. 2023

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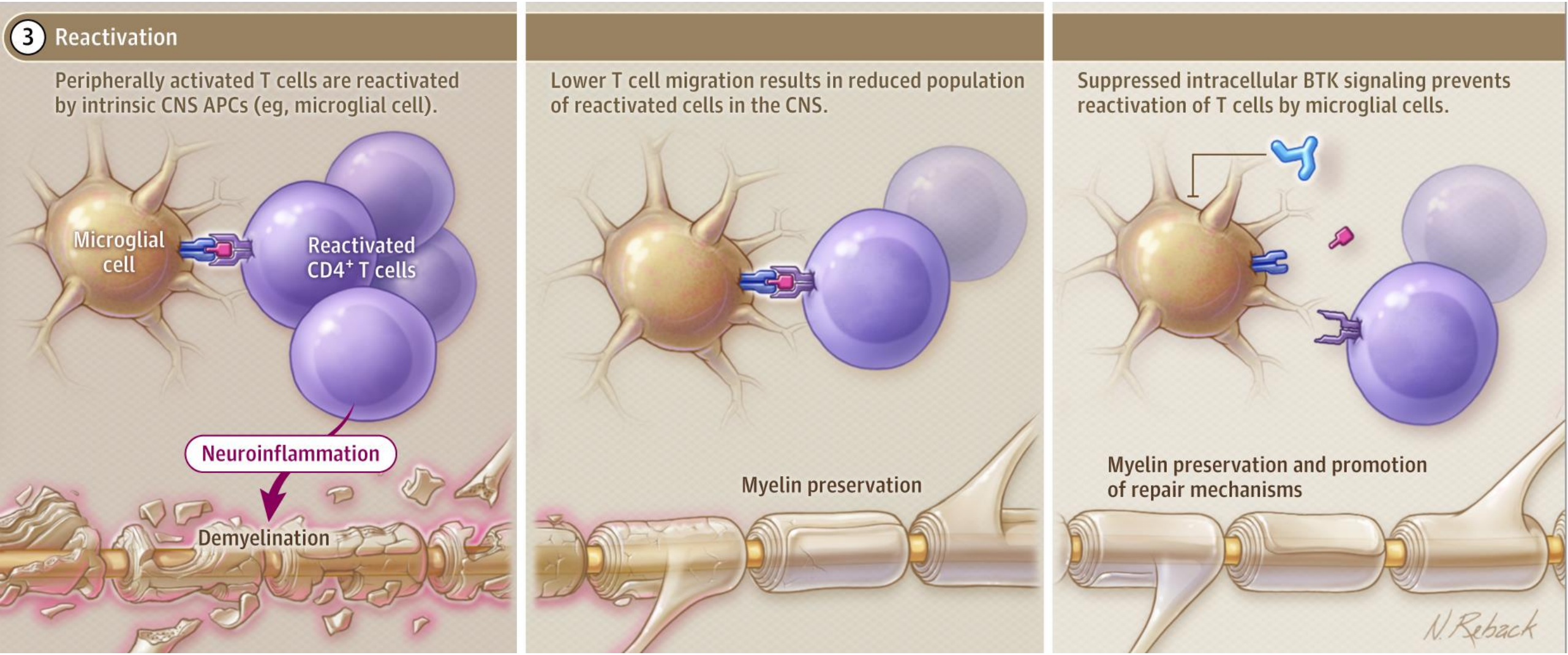


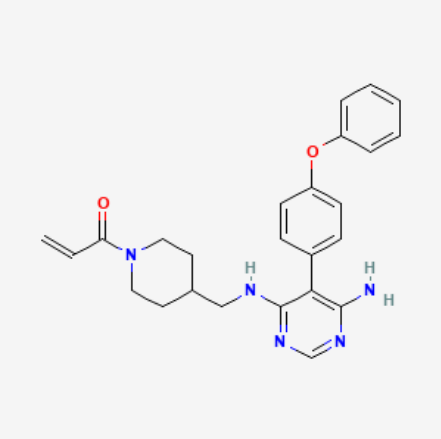
Dybowski et al. JAMA Neurol. 2023

Other differences

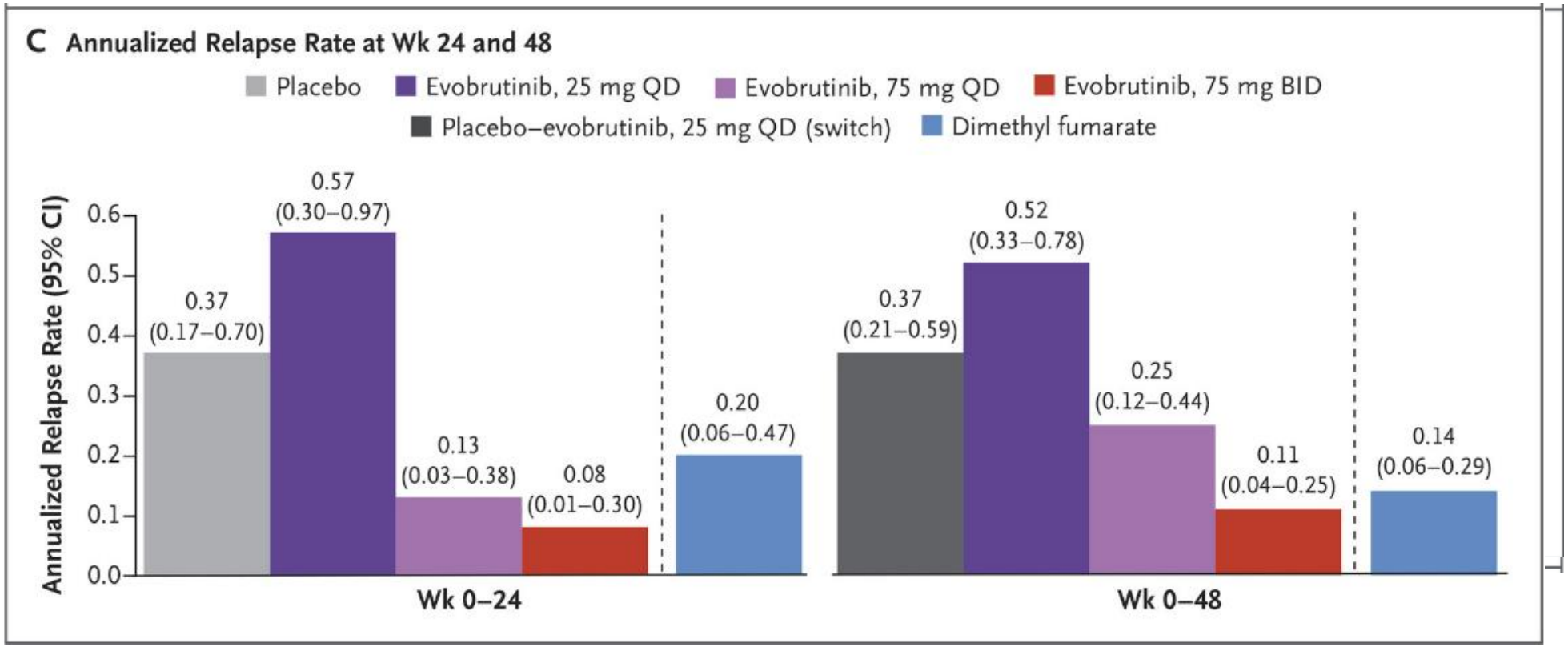
- Reversibility
  - Several months on anti-CD20
  - Several days on BTKi
- CNS penetration
  - 0.1% of plasma levels in CSF on anti-CD20
  - BTKis can penetrate CNS
  - Myelin repair
  - Progressive MS
- B-cell phenotype after therapy cessation
- Long-term effect on antibodies

Review of Clinical Trial Data

Evobrutinib



National Center for Biotechnology Information. "PubChem Compound Summary for CID 71479709, Evobrutinib" *PubChem*, https://pubchem.ncbi.nlm.nih.gov/compound/Evobrutinib. Accessed 5 May, 2023.



Phase 2, RMS or SPMS, dose-finding, placebo vs 25mg Qd vs 75mg Qd vs 75mg BID vs dimethyl fumarate
Blinded for 24 weeks, then blinded extension for 24 weeks (placebo switch to 25mg Qd)
Primary end point: Contrast enhancing lesions

Montalban et al. NEJM 2019

Evobrutinib

- Common adverse events: nasopharyngitis, elevations in liver and pancreatic function tests

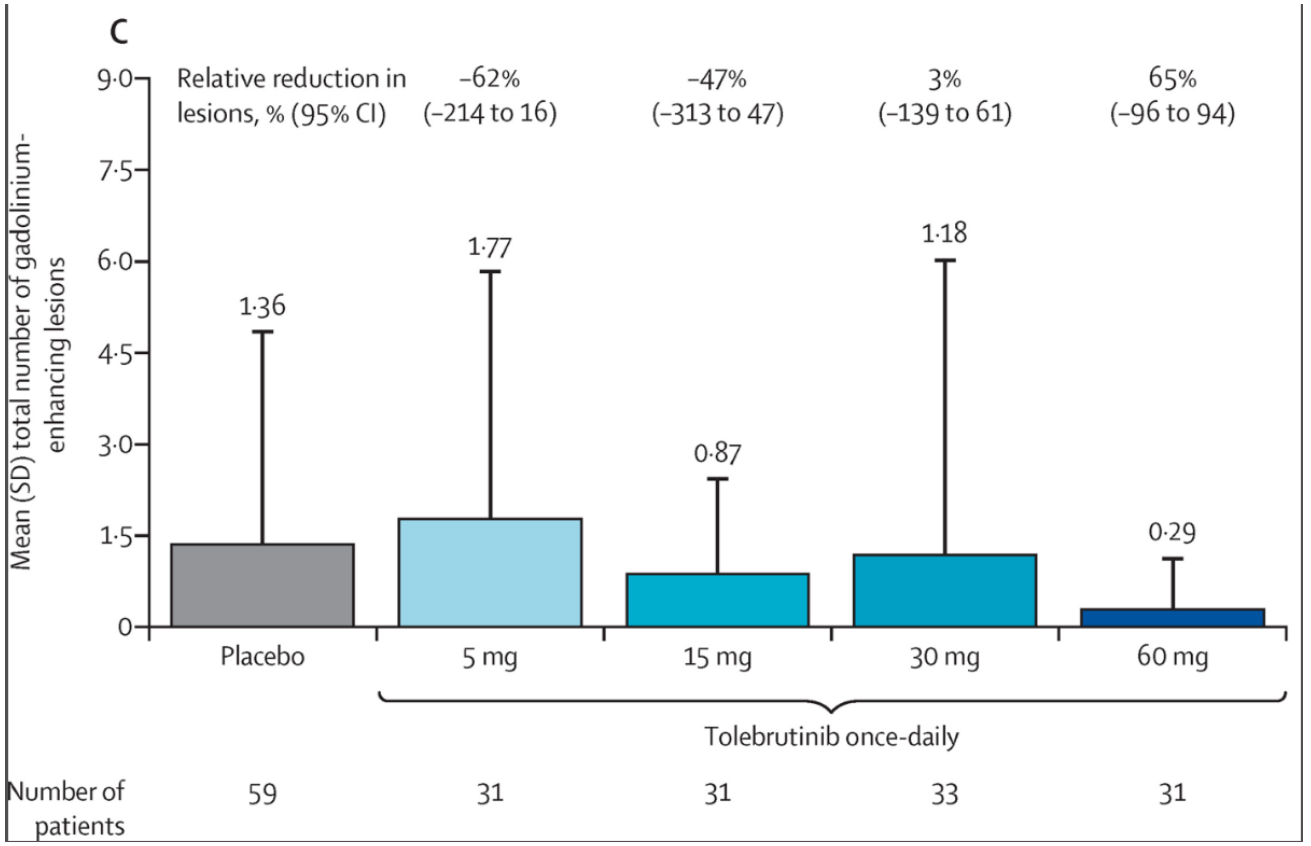
- Open label extension date up to 228 weeks (155/213): ARR remained low (0.13). No new safety signal.
- Reduced serum neurofilament light chain levels. Lower levels associated with improved MRI outcomes and relapse activity.

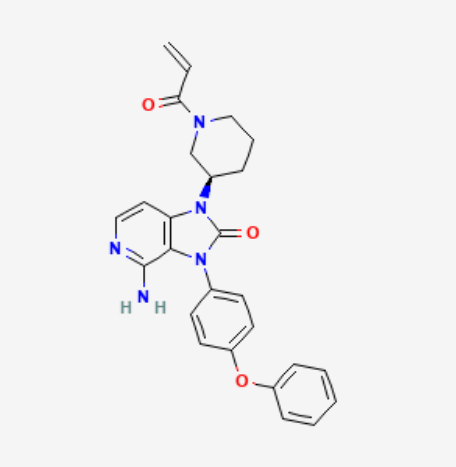
Table 3. Adverse Events at 52 Weeks (Safety Population).

Adverse Event	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)	Dimethyl Fumarate (N=54)
	number of patients (percent)				
Any adverse event	30 (56)	28 (54)	35 (66)	34 (63)	35 (65)
Any grade 3 or 4 adverse event†	6 (11)	1 (2)	7 (13)	8 (15)	7 (13)
Serious adverse event‡	2 (4)	2 (4)	2 (4)	4 (7)	2 (4)
Adverse event leading to discontinuation	5 (9)	3 (6)	6 (11)	7 (13)	2 (4)
Adverse event 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 adverse events¶					
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 aminotransferas	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)

Kuhle et al. ACTRIMS 2023; Montalban et al. NEJM 2019

Tolebrutinib





National Center for Biotechnology Information. PubChem Compound Summary for CID 124111565, Tolebrutinib. https://pubchem.ncbi.nlm.nih.gov/compound/Tolebrutinib. Accessed May 12, 2023.

Phase 2, RMS, dose-finding: placebo vs 5mg Qd vs 15mg Qd vs 30mg Qd vs 60mg Qd, cross over (12 weeks on drug, 4 week on placebo). Long ter extension

In 47% with highly active disease, 60mg Qd group had 0.93 relative total lesion reduction and 0.85 relative new enhancing lesions

Reich et al. Lancet Neurol. Sept 2021, Syed et al. AANAM 2021

Tolebrutinib

- Common side effects: Headache, elevated liver function testing
- 2 year extension study:
  - 90.5% patient remained
  - ARR 0.17, 80.6 % remained relapse free.
  - No new safety signal
  - Common AEs: COVID19, headache, nasopharyngitis, URI, bacterial cystitis, back pain, arthralgia

	All participants (n=130)	Tolebrutinib (n=130)			
		5 mg (n=33)	15 mg (n=32)	30 mg (n=33)	60 mg (n=32)
Participants with ≥1 adverse event					
Any adverse event	70 (54%)	19 (58%)	17 (53%)	18 (55%)	16 (50%)
Severe adverse events*	1 (1%)	0	0	0	1 (3%)
Serious adverse events*	1 (1%)	0	0	0	1 (3%)
Adverse events leading to death	0	0	0	0	0
Adverse events leading to study discontinuation	0	0	0	0	0
Any adverse event leading to study treatment discontinuation	0	0	0	0	0
Any treatment-related adverse event	17 (13%)	5 (15%)	1 (3%)	4 (12%)	7 (22%)
Adverse events 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 et al. Lancet Neurol. Sept 2021; Oh et al. AANAM 2023

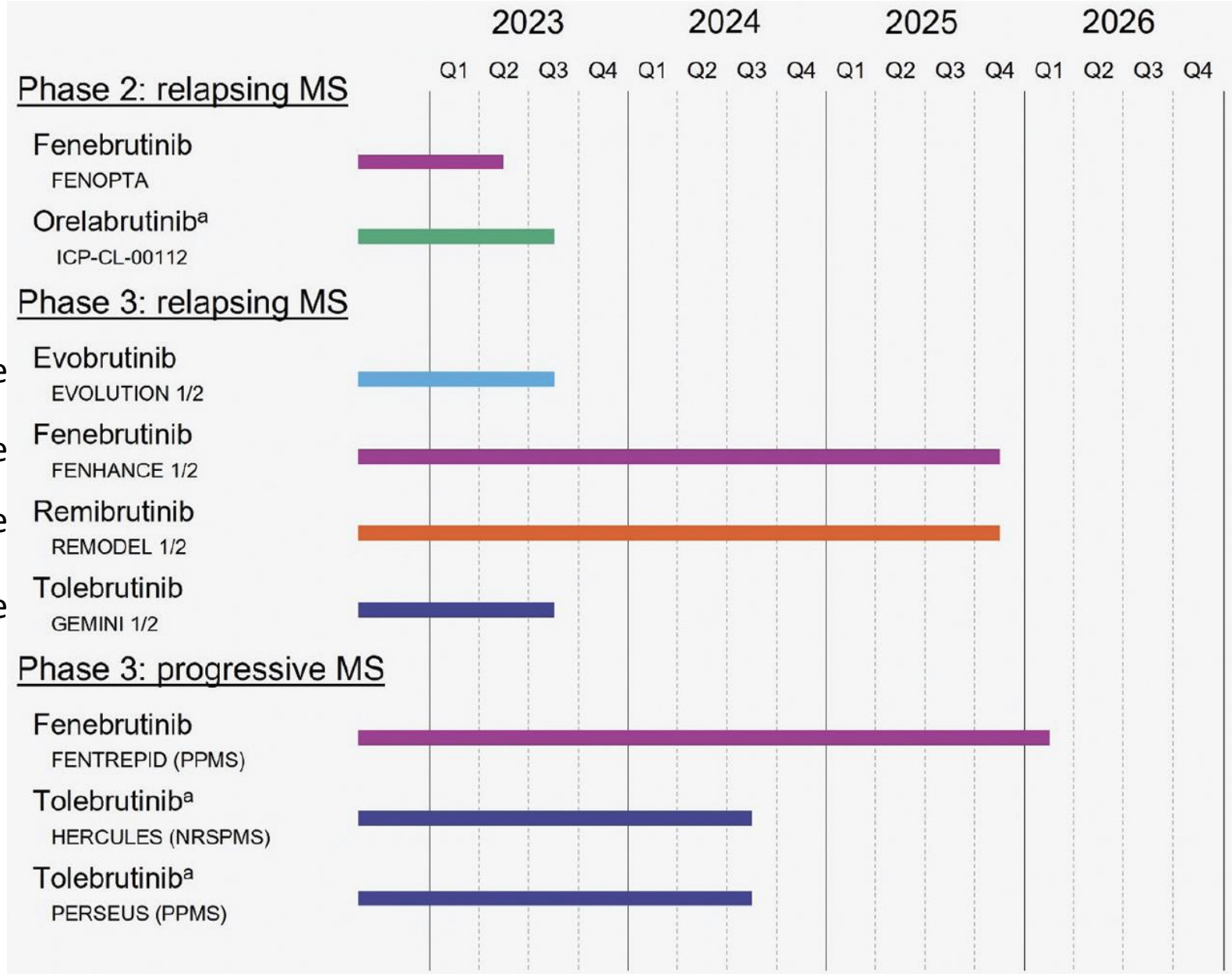


Figure adapted from Kolli et al. Practical Neurology. March 2023

Clinical considerations

Clinical considerations

- What differentiates one BTKi from another?
  - Selectivity, CNS penetration, chemical bond, binding site
- Vaccination effects
- Long term safety issues
- Where does BTKi fit in the current MS treatment landscape?
  - Target patient population
  - Combination or sequential therapy

Conclusion

Conclusion

- BTK inhibitors are part of a new group of immunomodulatory therapies being investigated for the treatment of relapsing and progressive MS
- BTK inhibitors target both adaptive and innate immune mechanisms and can penetrate the blood brain barrier
- BTK inhibitors have differential effects from anti-CD20 monoclonal antibodies
- Encouraging phase 2 trial results from evobrutinib and tolebrutinib suggest value of BTK inhibitors in the current MS treatment landscape
- Various phase 2 and 3 trials of BTK inhibitors are ongoing for RMS and PMS
- BTK inhibitors are heterogenous in terms of drug properties and may affect efficacy and safety

Questions