Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Targeting Bruton's Tyrosine Kinase (BTK) in Autoimmunity: Achievements, Opportunities and Challenges

Sebastian Torke[1,*], Sarah Dybowski[2,*], Martin S Weber[2–4]

[1]Experimental and Clinical Research Center, Charité-Medical Center Berlin and Max-Delbrück-Center for Molecular Medicine, Berlin, Germany; [2]Department of Neurology, University Medical Center Göttingen, Göttingen, Germany; [3]Institute of Neuropathology, University Medical Center Göttingen, Göttingen, Germany; [4]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Translational Neuroinflammation and Automated Microscopy TNM, Göttingen, Germany

*These authors contributed equally to this work

Correspondence: Martin S Weber, Department of Neurology, University Medical Center Göttingen, Göttingen, Germany, Tel +49-551 39-67087, Fax +49-551-39-10800, Email martin.weber@med.uni-goettingen.de

Abstract: The selective inhibition of Bruton's tyrosine kinase (BTK) has emerged as a promising therapeutic strategy for autoimmune diseases by targeting key signaling pathways in both adaptive and innate immune cells. Initially developed for B cell malignancies, BTK inhibitors are now being evaluated across a range of immune-mediated disorders, including multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. Beyond B cell receptor signaling, BTK inhibition modulates Fc receptor- and toll-like receptor-dependent activation of myeloid cells, thereby extending its therapeutic relevance. BTK inhibitors comprise a pharmacologically diverse class, including covalent (irreversible) and non-covalent (reversible) inhibitors, which differ in binding mode, selectivity, and pharmacokinetic properties. These differences are increasingly recognized as critical determinants of clinical performance. While early studies demonstrated robust target engagement and anti-inflammatory activity, clinical outcomes have been inconsistent across diseases. In multiple sclerosis, BTK inhibitors have shown promising effects on inflammatory activity and emerging signals on disability progression. In contrast, in rheumatoid arthritis and systemic lupus erythematosus, several compounds failed to meet primary clinical endpoints despite clear pharmacodynamic effects. These divergent outcomes highlight that the efficacy of BTK inhibition depends on disease-specific immune architecture and the relative contribution of BTK-dependent pathways. Safety considerations, including hepatotoxicity signals observed in late-stage trials, and differences between individual compounds further complicate clinical development. In this review, we summarize the mechanistic rationale of BTK inhibition, compare key pharmacological properties across BTK inhibitors, and critically assess clinical trial outcomes. We further discuss key challenges, including patient heterogeneity, trial design constraints, the lack of direct comparative studies, and outline future directions such as biomarker-driven patient selection and the development of BTK degraders.

Keywords: BTK inhibition, autoimmune diseases, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, PROTACs, molecular glue degraders

Introduction

Bruton's Tyrosine Kinase (BTK) was initially described in 1993 and named after Ogden C. Bruton who documented the first case of x-linked agammaglobulinemia (XLA), a disease caused by mutations in the BTK gene leading to an Immunoglobulin (Ig) deficiency and the lack of B- and plasma cells.[1] The BTK gene is located on the X chromosome and encodes a 659 amino acid long protein that functions as a key signaling component, most prominently involved within the B cell receptor (BCR) pathway, but also associated with Fc-receptor, toll-like-receptor and chemokine-receptor signaling.[2] As a member of the tyrosine kinase expressed in hepatocellular carcinoma (Tec)-family of kinases, BTK is expressed mainly in cells belonging to the hematopoietic system, such as B cells, dendritic cells, mast cells, neutrophils, macrophages, platelets and stem cells. Other

https://doi.org/10.2147/DDDT.S568214
Received: 25 February 2026
Accepted: 2 July 2026
Published: 14 July 2026

members of the Tec family are the kinases: interleukin (IL) 2-inducible T cell kinase (ITK), tyrosine kinase expressed in hepatocellular carcinoma (Tec), resting lymphocyte kinase (RLK) as well as bone-marrow tyrosine kinase gene on the X chromosome (BMX). Structurally, all members of the Tec family present with a kinase domain at the C-terminus and various regulatory and protein binding domains towards the N-terminus.[3,4]

Principle of BTK Inhibition

Because of its lineage expression within B cells and its key role within the BCR signaling pathway—regulating B cell proliferation, maturation and function—BTK became a target for functional inhibition. Mechanistically, BTK inhibitors can be categorized into ones that exert a covalent bond with the protein, most commonly called irreversible inhibitors, and such inhibitors which bind BTK in a reversible manner. The binding mechanism, eg. for ibrutinib, features an acrylamide group of the inhibitor interacting with the cysteine residue C481 within the kinase domain of BTK, thereby disrupting efficient kinase activity and downstream signaling relay. Later developed inhibitors of the second or third generation will still target the active site of the enzyme but might bind to other residues.[5]

The first BTK inhibitor recognized by the Federal Drug Administration (FDA) was ibrutinib, which in 2013 was approved for the treatment of mantle cell lymphoma (MCL). Subsequently, ibrutinib was also approved for marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL) and Waldenström's macroglobulinemia (WM). Furthermore, ibrutinib was the first treatment to receive approval in graft-versus-host disease (GvH). Second generation inhibitors generally show reduced off-target effects by lower affinities towards eg. Tec, EGF or Src family kinases when compared to ibrutinib.[6] Overall, the class of BTK inhibitors displays comparable tolerability in patients, with the most common adverse events being bleeding, increased infection risks, cardiac arrhythmias, and skins disorders.[2,6]

To date, six BTK inhibitors have been approved by the FDA in the United States, by date of approval: ibrutinib (11/2013), acalabrutinib (10/2017), zanubrutinib (11/2019), pirtobrutinib (01/2023), rilzabrutinib (08/2025) and remibrutinib (09/2025). One other molecule—orelabrutinib—is approved in China. Most approved BTK-targeting drugs are used in B cell malignancies, with the exception of remibrutinib and rilzabrutinib, which are posed for the therapy of chronic spontaneous urticaria and persistent or chronic immune thrombocytopenia, respectively. Furthermore, a large number of inhibitors are currently being investigated in pre-clinical as well as clinical trials (Table 1).

Table 1 BTK Inhibitors in Clinical Trials in Different Inflammatory Diseases

Disease	BTK Inhibitor	Key Trials & Current Status	ClinicalTrials.gov ID
Multiple Sclerosis	Evobrutinib	Phase II in RMS showed MRI lesion reduction Phase III in RMS failed to meet primary endpoints of ARR against teriflunomide	NCT02975349 NCT04338022, NCT04338061
	Fenebrutinib	Phase III positive in RMS vs teriflunomide Phase III in PPMS comparable to ocrelizumab	NCT04586023 NCT04544449
	Orelabrutinib	Phase II in RRMS showed reduction of ARR and MRI activity vs placebo	NCT04711148
	Remibrutinib	Phase II in RMS showed MRI lesion reduction Phase III in RMS vs teriflunomide is ongoing	NCT05147220 NCT05156281
	Tolebrutinib	Phase III in RMS failed to meet primary endpoints of ARR against teriflunomide Phase III in PPMS vs placebo not yet published Phase III in non-relapsing SPMS significantly delayed disability progression vs placebo	NCT04410978, NCT04410991 NCT04458051 NCT04411641

(*Continued*)

Table 1 (Continued).

Disease	BTK Inhibitor	Key Trials & Current Status	ClinicalTrials.gov ID
Rheumatoid Arthritis	Evobrutinib	Phase IIb in MTX-IR RA had no meaningful ACR20/50 benefit	NCT03233230
	Fenebrutinib	Phase II MTX-IR RA compared to placebo and adalimumab the ACR50 was similar to adalimumab: no Phase III progression	NCT02833350
	Poseltinib (HM71224)	Phase II in active RA vs placebo terminated early for futility	NCT02628028
	Sprebrutinib	Phase II in active RA in co-therapy with MTX vs placebo was well tolerated and improved symptoms	NCT01975610
	Branebrutinib	Phase II in active RA/SLE/SjS vs abatacept and placebo, data not yet published	NCT04186871
	BMS-986142	Phase II in moderate to severe RA compared to placebo and MTX no clinical benefit	NCT02638948
Systemic Lupus Erythematosus	Evobrutinib	Phase II in SLE had no significant benefit (SRI-4/BICLA) vs placebo	NCT02975336
	Fenebrutinib	Phase II in moderate to severe active SLE vs placebo did not meet primary endpoints of SRI-4 response	NCT02908100
	Orelabrutinib	Phase IIb in SLE improved SRI-4 response in high dose cohort vs placebo and met the primary endpoint	NCT05688696
Sjögren's Syndrome	Remibrutinib	Phase II in severe SjS improved ESSDAI vs placebo	NCT04035668
Pemphigus Vulgaris/ Atopic Dermatitis	Rilzabrutinib	Phase II pilot study for safety were positive Phase III failed to meet primary endpoint the achievement of complete remission with minimal corticosteroids vs placebo Phase II in moderate to severe atopic dermatitis vs placebo	NCT02704429 NCT03762265 NCT05018806
Chronic Spontaneous Urticaria	Fenebrutinib	Phase II in antihistamine-refractory CSU vs placebo showed significant efficacy; further clinical trials are not planned as development has shifted toward other autoimmune diseases	NCT03693625
	Remibrutinib	Phase II and Phase III met co-primary endpoints compared to placebo; approvals in regions underway	NCT05030311, NCT05032157
	Rilzabrutinib	Phase II showed efficacy and safety vs placebo	NCT05107115
Immune Thrombocytopenia	Rilzabrutinib	Phase II/III showed rapid platelet responses vs placebo; ongoing Phase III	NCT04562766
	Orelabrutinib	Phase II study in refractory ITP with unknown status	NCT05020288
IgG4-related disease	Rilzabrutinib	Phase II study showed positive IgG4-RD reductions (EMA orphan designation) vs glucocorticoids	NCT04520451
Generalized Myasthenia Gravis	Remibrutinib	Phase II showed positive results vs placebo; ongoing Phase III	NCT06744920
Systemic Sclerosis	Tirabrutinib	Phase I safety/PK exploration	jRCT2031200315
Asthma	Rilzabrutinib	Phase II proof of concept study vs placebo	NCT05104892

Pharmacological Properties and Safety of BTK Inhibitors

BTK inhibitors represent a structurally and pharmacologically heterogeneous class of small molecules, despite sharing a common molecular target. Differences in binding mode, selectivity, reversibility, and tissue distribution translate into distinct pharmacodynamic and clinical profiles, which likely contribute to the heterogeneous outcome across autoimmune diseases.

A central distinction within the BTK inhibitors lies in the target binding, dividing compounds into covalent (irreversible) and non-covalent (reversible) inhibitors. Covalent BTK inhibitors, such as evobrutinib, tolebrutinib, and remibrutinib, form an irreversible bond with the cysteine residue (Cys481) in the ATP-binding pocket of BTK, resulting in sustained target occupancy even after systemic drug clearance.[7] This allows for prolonged pathway inhibition with relatively low plasma exposure but may increase the risk of off-target interactions with kinases harboring homologous cysteine residues. The reliance of covalent inhibitors on Cys481 also represents a potential mechanistic vulnerability. In oncology settings, resistance to ibrutinib has been linked to mutations at this residue, preventing irreversible binding and restoring BTK signaling.[8,9] Although such mechanisms have primarily been described in malignant B cell diseases, they illustrate fundamental differences in binding dependency that may also be relevant for long-term therapeutic strategies. In contrast, non-covalent inhibitors such as fenebrutinib bind reversibly and independently of Cys481, allowing for greater flexibility and potentially improved kinase selectivity. Their activity is not affected by Cys481 mutations, but effective inhibition depends on continuous systemic exposure to maintain effective pathway suppression.

In addition to binding mode, BTK inhibitors differ in their intrinsic potency, typically expressed as the half-maximal inhibitory concentration IC50. Many next-generation inhibitors exhibit nanomolar or sub-nanomolar potency against BTK, reflecting strong enzymatic inhibition. However, biochemical potency alone does not fully predict biological or clinical efficacy. Cell-based assays and clinical pharmacodynamic studies indicate that effective pathway inhibition depends not only on IC50 but also on target occupancy, drug exposure, and tissue distribution.

Selectivity among BTK inhibitors represents another key differentiator and has improved substantially over generations of development. First-generation inhibitors, exemplified by ibrutinib, exhibit broad kinase inhibition, including targets such as EGFR, ITK, and TEC family kinases, which has been associated with adverse events such as bleeding, atrial fibrillation, and infections in oncology settings.[10] Newer BTK inhibitors developed for autoimmune diseases have been optimized for greater selectivity, reducing off-target kinase interactions and improving tolerability at lower doses.[11]

Beyond binding characteristics and selectivity, tissue distribution – particularly central nervous system (CNS) penetration – has emerged as a critical property. CNS-penetrant BTK inhibitors are capable of crossing the blood-brain barrier and directly modulating microglial activation, thereby targeting compartmentalized inflammation that is largely inaccessible to monoclonal antibody therapies.

The safety profile of BTK inhibitors reflects both on-target immunomodulation and compound-specific off-target effects. Across autoimmune disease trials, BTK inhibitors have generally demonstrated favorable tolerability compared with other therapeutics in the oncology settings, likely due to lower dosing and improved selectivity. However, hepatoxicity has emerged as a relevant safety signal across multiple compounds. Transient elevations in liver enzymes led to temporary clinical holds in late-stage trials of tolebrutinib[12] and have also been reported with evobrutinib,[13] suggesting that this may represent a broader class-related liability. Importantly, in controlled studies, the frequency of transaminase elevations observed with tolebrutinib was comparable to that seen with teriflunomide,[14] indicating that magnitude of this signal may not exceed that of established therapies. At the same time, variability between compounds suggests that hepatotoxicity may also be influenced by molecule-specific properties. Other class-associated risks include infections due to modulation of B cell and innate immune pathways, whereas bleeding tendencies and cardiovascular events, which were well described for earlier less selective BTK inhibitors such as Ibrutinib in oncology, appear less pronounced with newer, more selective compounds used at lower doses in autoimmune diseases. Together, these observations indicate that while certain safety signals may represent class effects, the overall risk profile of BTK inhibition is strongly influenced by compound-specific properties such as selectivity, binding mode, and pharmacokinetics.

B Cell Malignancies

BTK plays a crucial role within the BCR signaling pathway and therein is an essential element not only for B cell survival but also proliferation, function and interactions with other cell types. B cell-derived cancers can be subclassed by their origin as the neoplastic cells originate either from the bone marrow (leukemia) or arise within secondary lymphoid structures (lymphomas). CLL is the most common type of leukemia in the west and displays an accumulation of mature B cells with chronically active BCR signaling in the circulatory system.[15] This is highlighted by an autonomous mobilization of excitatory calcium in the absence of BCR ligands in isolated B cells from CLL patients.[16] Therefore,

interrupting this disease-driving pathway by interfering with BTK signal relays has proven a successful strategy for the therapy in this malady. Inhibition of BTK signals has shown to reduce CLL cell survival by affecting essential BTK-dependent pathways such as AKT, ERK and NF-κB.[17]

B cells from MCL patients display a strong phosphorylation of Y223, a key position necessary for BTK activation and signaling, a disease-driving mechanism that was reversible by interfering with BTK signaling through ibrutinib treatment.[18] Moreover, BTK inhibition is capable of mediating the retention of B cells within the lymphoid structures as it regulates the egress of cells into the periphery.[19]

The most common cause of WM are mutations within the MyD88 gene at position 265 of the amino acid chain[20] as well as alterations in CXCR4 signaling. The activating MyD88 mutation drives disease by forming active signaling complexes within the TLR cascade, in which BTK is also actively involved.[21] Moreover, interactions of mutated MyD88 with phosphorylated BTK are capable of triggering NF-κB signaling and inducing pro-survival signals.[22] In more than 90% of WM patients harboring the MyD88 L265P mutation, both BTK as well as NF-κB signaling pathways are constitutively activated.[2] Accordingly, BTK inhibition has emerged as one of the standard treatments of WM.[21]

Importantly, BTK inhibitors were not initially developed to target B cell malignancies. The targeting of BTK, because of its central role in the aforementioned signaling pathways and its key regulation of B cell-mediated immunity, was initially designed for the therapy of autoimmune diseases. Specifically, ibrutinib was originally posed as a novel therapeutic in rheumatoid arthritis (RA), aiming to rival the B cell targeting antibody rituximab.[23] Subsequently, based on its broad inhibitory effects on immune-mediated pathology, the scope of BTK inhibitors was expanded towards Multiple Sclerosis (MS), Systemic Lupus Erythematosus (SLE) and other immunological malignancies such as Sjögren's Syndrome. Elucidating current perspectives on the role of BTK inhibition in autoimmune diseases will be the main focus of this review from this point forward.

Multiple Sclerosis

Rationale for Targeting BTK in MS

MS is a chronic inflammatory and neurodegenerative disease of the CNS, characterized by immune-mediated demyelination, axonal injury, and progressive neurological disability.[24,25] The pathology of MS involves both acute inflammatory events, which drive relapses and new lesion formation, and slow compartmentalized inflammation within the CNS, which contributes to chronic lesion evolution and long-term disease progression.[26,27] Current disease-modifying therapies (DMTs) are highly effective in reducing peripheral inflammatory activity and relapse rates, yet many patients continue to accumulate disability, particularly as the disease transitions into its progressive phases.[28,29] This unmet need reflects limitations of therapies that primarily target the peripheral adaptive immune system without sufficiently addressing CNS-resident innate immune mechanisms, such as chronic microglial activation.[30,31]

Unlike anti-CD20 monoclonal antibodies, which primarily deplete circulating B cells, BTK inhibition modulates both non-depleted B cells and myeloid-lineage cells, including macrophages and microglia.[32,33] Several studies have shown BTK expression within active MS lesions and at sites of leptomeningeal inflammation, supporting the rationale for targeting this kinase to reduce not only acute inflammatory activity but also smoldering inflammation contributing to disability progression.[34] In addition, certain BTK inhibitors are designed to penetrate the CNS, allowing pharmacological modulation of microglia activation – an emerging therapeutic target in progressive MS (Figure 1).

Thus, BTK inhibition has been proposed as a strategy capable of bridging two therapeutic needs in MS: rapid reduction of relapse-driven inflammation and long-term attenuation of chronic progression.

Preclinical Evidence

Preclinical studies in experimental autoimmune encephalomyelitis (EAE) and cuprizone-induced demyelination models provide strong mechanistic support for BTK inhibition. Using putative protein tyrosine kinase inhibitors, such as tyrphostin AG126, reduced clinical symptoms, CNS infiltration, microglial activation and myelin damage as well as the differentiation of encephalitogenic Th17 T cells in an EAE model, an effect attributed to the effective inhibition of BTK.[35] Generally, specific inhibition of BTK reduced B cell activation and antigen presentation and diminished Fc-receptor-mediated activation of innate immune cells.[36] In EAE models, BTKi attenuated disease severity, reduced CNS infiltration of lymphocytes and

suppressed meningeal inflammation.[37] Recent studies have shown that BTK inhibition not only suppressed pro-inflammatory B cell activation but also shifted the B cell compartment toward B cells with regulatory properties.[38] Providing evidence that BTK inhibition potentially enhances immune tolerance while reducing T cell-driven inflammation in EAE models, suggesting a balanced immunomodulatory rather than purely suppressive effect (Figure 1).

Beyond peripheral immune modulation, several studies have shown that CNS-penetrant BTKi directly affect microglial activation and shift microglial transcriptional profiles toward a less inflammatory, more homeostatic state.[39,40] This has been shown to improve clearance of myelin debris, reduce the release of neurotoxic mediators, and create a more permissive microenvironment for remyelination and tissue repair.

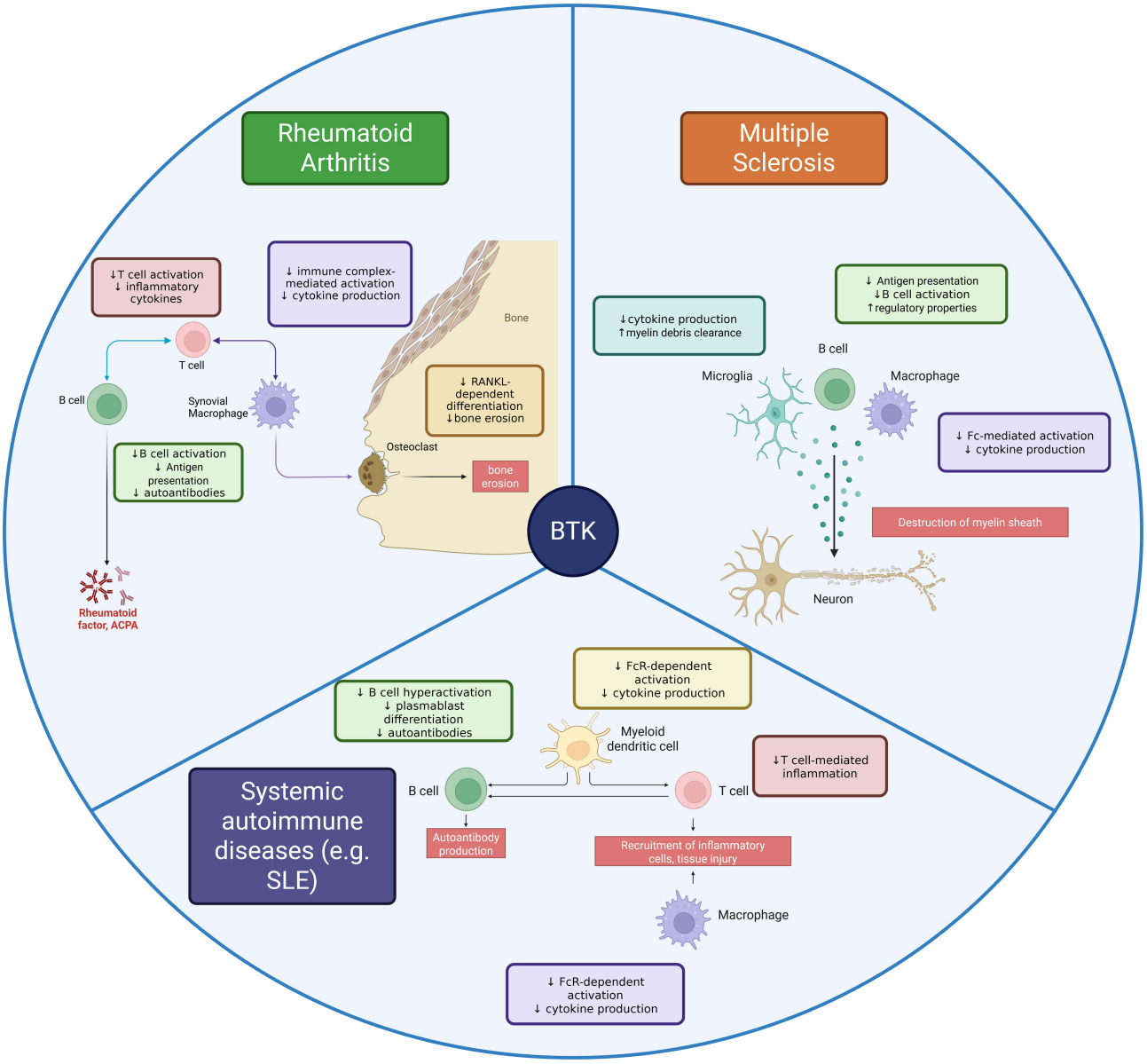

Figure 1 Effects of BTK inhibition in autoimmune diseases. Alterations induced by BTK inhibition in rheumatoid arthritis, multiple sclerosis and systemic autoimmune diseases such as systemic lupus erythematosus (SLE). Increases indicated by ↑, decreases by ↓.

https://doi.org/10.2147/DDDT.S568214

Clinical Development of BTK Inhibitors in MS

Evobrutinib

Evobrutinib was the first BTK inhibitor tested extensively in MS. In a Phase II trial in relapsing MS (RMS), evobrutinib produced significant reductions in gadolinium-enhancing MRI lesions, particularly at the highest dose, demonstrating a clear anti-inflammatory pharmacodynamic effect.[41] However, the study did not show statistically significant reductions in annualized relapse rate (ARR) or disability measures compared with placebo. Long-term extension data confirmed sustained MRI suppression and adequate tolerability, but the subsequent Phase III program failed to meet its clinical primary endpoint.[42] The contrast between strong MRI activity and limited clinical benefit highlighted the challenge of translating radiographic effects to meaningful relapses or disability outcomes.

Tolebrutinib

Tolebrutinib is a covalent, CNS-penetrant BTK inhibitor specifically optimized for brain bioavailability. A phase II dose-finding study in relapsing MS demonstrated a robust, dose-dependent reduction in new enhancing MRI lesions.[43] Early enthusiasm was tempered by safety concerns related to liver enzyme elevations, leading to temporary clinical holds. More recently, large phase III trials in relapsing MS found that tolebrutinib was not superior to teriflunomide in reducing relapses.[14]

However, tolebrutinib produced a major breakthrough in the progressive MS space: the phase III HERCULES trial in non-relapsing secondary progressive MS demonstrated a significant reduction in confirmed disability progression, making it the first BTK inhibitor to show compelling evidence for progression modification.[44] This result supports the concept that BTK inhibition, particularly with CNS-penetrant agents, may modulate the innate immune drivers of neurodegeneration.

Fenebrutinib

Fenebrutinib is a highly selective, reversible BTK inhibitor and is currently the most advanced molecule in development. Early phase II studies demonstrated reduction of MRI lesion activity in relapsing MS,[45] and the larger phase III program delivered strongly positive results in both relapsing MS and primary progressive MS.[46,47] In relapsing disease, fenebrutinib significantly reduced ARR versus teriflunomide; in primary progressive MS, it achieved favorable disability outcomes comparable in effect strength to ocrelizumab. These data position fenebrutinib as a frontrunner among BTK inhibitors, distinguishing it from earlier agents that produced inconsistent clinical benefit.

Remibrutinib

Remibrutinib is another highly selective covalent inhibitor with an excellent safety profile demonstrated in other autoimmune indications. Phase III trials in relapsing MS are ongoing. While no MS efficacy results have yet been published, remibrutinib's strong clinical performance in chronic spontaneous urticaria[48] and Sjögren's syndrome[49] suggests potential utility across immune-mediated diseases, including MS.

Orelabrutinib

Orelabrutinib is a highly selective, CNS-penetrant BTK inhibitor with established use in hematologic malignancies. In a phase II study in relapsing-remitting MS, orelabrutinib produced robust MRI efficacy, with the 80 mg dose reducing new gadolinium-enhancing T1 lesions by approximately 90% versus placebo over 24 weeks.[50] While clinical relapse and disability outcomes remain to be established, these data support effective target engagement within the CNS and have informed ongoing phase III development.[51]

Summary

Early findings from tolebrutinib and fenebrutinib provide important proof-of-concept insights that BTK inhibitors may become the first oral agents of influencing progression independent of relapses. By targeting both B cell activity and microglial activation, BTK inhibition introduces a mechanistically distinct strategy compared to current DMTs, with next-generation, CNS-penetrant compounds showing the greatest promise for addressing neurodegeneration. At the same time, recent trials highlight that substantial MRI lesion reductions do not necessarily translate into clinical benefit, as seen with evobrutinib and early tolebrutinib studies. Safety remains a key consideration: hepatotoxicity has emerged for

certain BTK inhibitors, and class-wide risks – although milder at doses commonly used in other autoimmune diseases – require continued vigilance. Given the high efficacy of anti-CD20 therapies, the ability of BTK inhibition to meaningfully slow progression offers a promising opportunity for this drug class to establish a valuable and differentiated role in MS treatment.

Rheumatoid Arthritis

Rationale for Targeting BTK in Rheumatoid Arthritis

RA is a chronic systemic autoimmune disease characterized by persistent synovial inflammation, autoantibody production such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), and progressive destruction of cartilage and bone. The pathogenesis of RA is complex and involves a dynamic interplay between innate and adaptive immune responses. B cells and myeloid cells are central to disease development and progression, not only through autoantibody production but also via antigen presentation, secretion of pro-inflammatory cytokines, formation of immune complexes, and activation of osteoclasts, which collectively drive joint damage (Figure 1).

Despite significant advances in treatment including the introduction of TNF inhibitors, IL-6 receptor antagonists, and JAK inhibitors, a considerable proportion of patients fail to achieve sustained remission or experience inadequate disease control. This therapeutic gap emphasizes the need for novel approaches targeting alternative pathways, particularly those involving B cells and innate immune mechanisms.

Preclinical Evidence

Preclinical studies in RA models have demonstrated that BTK inhibition effectively modulates several key pathogenic pathways driven by B cells, synovial macrophages, and immune-complex-driven myeloid cell activation. In both collagen-induced arthritis (CIA)[52] and K/BxN serum-transfer[53] models, BTK inhibition reduced B cell receptor–mediated activation, autoantibody production (RF, ACPA-like antibodies), and B cell antigen presentation.[54] These effects lead to decreased downstream T cell activation and lower inflammatory cytokine production within the joint.

Studies have also demonstrated that BTK is essential for immune-complex-mediated activation of synovial macrophages.[55] BTK inhibition suppressed the production of TNF, IL-6, and IL-1β and reduced activation of NF-κB/MAPK pathways, thereby effectively reducing synovial inflammation.[56] Furthermore, BTK inhibition impaired RANKL-dependent osteoclast differentiation, which resulted in decreased bone erosion and better preservation of cartilage.

Clinical Studies of BTK Inhibition in RA

Fenebrutinib (GDC-0853)

The phase II ANDES trial represents the most robust clinical evidence to date for BTK inhibition in RA.[57,58] In this study, over 480 patients with an inadequate response to methotrexate (MTX-IR) were randomized to receive multiple doses of fenebrutinib, placebo, or adalimumab over a 12-week period. The primary endpoint, achievement of ACR50 at week 12, was met: fenebrutinib demonstrated response rates comparable to adalimumab and was clearly superior to placebo in the MTX-IR population. Notably, clinical activity was also observed, though to a lesser extent, in patients with prior inadequate response to TNF inhibitors. The safety profile of fenebrutinib was generally similar to that of placebo and adalimumab, with no new concerning signals. Despite these encouraging efficacy profile and safety data, the development program for fenebrutinib in RA did not advance to Phase III, likely due to strategic and competitive considerations given the established efficacy of TNF inhibitors, IL-6 blockade, and JAK inhibitors in this indication, rather than any specific safety concern.

Evobrutinib

By contrast, the phase IIb study of evobrutinib in MTX-IR RA patients failed to demonstrate meaningful clinical benefit.[59] Over 12 weeks, evobrutinib did not improve ACR20 or ACR50 responses compared to placebo, and the trial was interpreted as negative for efficacy. Integrated safety analysis across autoimmune populations, including RA, confirmed an acceptable safety profile but provided no rationale to pursue RA development further.

Poseltinib (HM71224/LY3337641)

The phase II trial of poseltinib in MTX-IR RA was terminated early after an interim analysis indicated a low probability of meeting the ACR20 primary endpoint.[60] Although the drug did not show major safety concerns, the lack of efficacy halted further investigation in RA.

BMS-986142

BMS-986142, a reversible BTK inhibitor, was evaluated in a dose-ranging, placebo-controlled phase II study.[61] Modest improvements were observed in certain clinical and imaging endpoints, but the primary endpoint was not consistently met across doses. Consequently, RA development of this compound appears to have been deprioritized.

Summary

Across multiple phase II trials, BTK inhibitors including fenebrutinib, evobrutinib, poseltinib, BMS-986142, and earlier exploratory work with acalabrutinib have yielded mixed or largely negative results in RA. Fenebrutinib stands out as the only compound demonstrating clinically meaningful efficacy comparable to a TNF inhibitor, yet this was insufficient to shift the therapeutic landscape. The overall experience highlights that RA pathogenesis is driven strongly by T cell-dependent and cytokine-driven pathways (TNF, IL-6, JAK/STAT), which are already well targeted by existing therapies. As a result, the benefit-risk and competitive profile for BTK inhibitors in RA has been less compelling than in other autoimmune diseases. This makes RA an instructive counterexample in the review: the same molecular target shows excellent translational promise in MS and possibly SLE but delivers limited therapeutic impact in RA, emphasizing the disease-specific biology of BTK dependence.

Systemic Lupus Erythematosus

Rationale for Targeting BTK in Systemic Lupus Erythematosus

SLE is a heterogeneous autoimmune disease characterized by dysregulated B cell activation, autoantibody production, immune-complex-mediated tissue injury, and aberrant myeloid cell activation.[62] BTK plays a central role in several of these pathogenic pathways, integrating signals from the B cell receptor and Fcγ receptors. By modulating B cell activation, plasmablast differentiation, antigen presentation, and innate immune responses, BTK occupies a key node in both adaptive and innate immune circuits (Figure 1).[63] Reviews emphasize that these mechanistic insights, combined with strong preclinical efficacy in lupus models, initially made SLE appear an ideal indication for BTK-targeted therapy.[64,65] However, early clinical trials have highlighted challenges related to patient heterogeneity and endpoint sensitivity, illustrating the difficulty of translating mechanistic promise into broad clinical benefit.[66]

Preclinical Evidence

Preclinical studies have consistently demonstrated that BTK inhibition modulates core pathogenic mechanisms in SLE. In lupus-probe mouse models, including NZB/W F1, MRL/lpr, and pristane-induced lupus, BTK inhibition reduced B cell hyperactivation, plasmablast differentiation, and autoantibody production (eg., anti-dsDNA), thereby mitigating T cell-mediated inflammation.[62] BTK inhibition also suppressed Fcγ receptor-dependent activation of macrophages and dendritic cells, lowering pro-inflammatory cytokines such as TNF, IL-6, and type I interferons and reducing immune-complex-driven organ injury. Notably, BTK inhibition ameliorated nephritis, decreased proteinuria, and improved renal histopathology, while also protecting skin and vascular tissues. Together, these studies provide a strong mechanistic rationale for BTK inhibition in SLE.

Clinical Studies of BTK Inhibition in SLE

Fenebrutinib

The phase II ATHOS trial evaluated fenebrutinib in 260 patients with moderate-to-severe SLE on standard-of-care therapy.[67] Over 48 weeks, multiple doses were compared with placebo using SRI-4 and BICLA as primary endpoints. The trial did not meet its primary endpoints, showing no significant differences versus placebo in global clinical response. Nevertheless, clear

pharmacodynamic effects were observed, including reductions in CD19+ B cells and anti-dsDNA antibodies. High placebo responses and patient heterogeneity may have obscured efficacy.

Evobrutinib

A phase IIb dose-ranging study tested evobrutinib over 52 weeks in adults with SLE on standard therapy.[68] Similar to fenebrutinib, the trial did not demonstrate significant improvement in SRI-4 or BICLA responses at any dose level. The drug was generally well tolerated and showed no dose-limiting toxicity. The absence of clinical benefit in key composite endpoints led to discontinuation of its development for SLE.

Orelabrutinib

Orelabrutinib is a highly selective, CNS-penetrant BTK inhibitor with favorable pharmacokinetics, and its development in SLE has generated renewed interest. In a phase Ib/IIa randomized controlled trial,[69] 60 patients received orelabrutinib at 50, 80, or 100 mg or placebo for 12 weeks. While the overall population showed modest improvements, a clear efficacy signal emerged in the subgroup with high disease activity (SLEDAI-2K > 8). In this cohort, SRI-4 responses were markedly higher with orelabrutinib, including up to 100% response at the highest dose, compared with 0% in the placebo group. The treatment was well tolerated, with mostly mild adverse events. These results suggest that BTK inhibition may exert meaningful clinical effects in mechanistically enriched, high-activity SLE populations. Larger phase IIb and phase III trials are now ongoing to validate these observations.[70]

Summary

Preclinical evidence clearly demonstrated that BTK inhibition modulates B cell and myeloid cell pathways, reducing autoantibody production and protecting target organs in lupus models. Clinically, fenebrutinib and evobrutinib have shown strong biomarker effects but failed to improve global endpoints in broad SLE populations. In contrast, orelabrutinib studies provided early evidence of clinical efficacy in patients with high disease activity. The collective experience emphasizes that BTK is biologically relevant in SLE, but patient heterogeneity and insensitive composite endpoints may obscure therapeutic benefit. Optimal patient selection, mechanistically informed trial design, and potential combination strategies may be required to fully exploit BTK inhibition in SLE.

Other Autoimmune Diseases (Sjögren's Syndrome, Pemphigus, CSU, ITP, and Others)

Rationale for Targeting BTKi in Other Autoimmune Diseases

Beyond MS, RA, and SLE, BTK-dependent signaling pathways play a critical role in several antibody- and immune complex-mediated autoimmune diseases. Many of these conditions share key features such as B cell hyperactivity, autoantibody production, Fc receptor-mediated activation of innate immune cells, and downstream tissue damage.[62] This positions BTK inhibition as a mechanistically attractive strategy in diseases including primary Sjögren's syndrome, pemphigus vulgaris, chronic spontaneous urticaria, and immune thrombocytopenia. Compared with broad immunosuppression, BTK inhibitors offer the potential for targeted modulation of disease-relevant immune circuits while preserving overall immune competence (Figure 1).

Preclinical Evidence

Preclinical studies across diverse disease models provide strong mechanistic support for BTK inhibition in antibody-driven autoimmunity. In models of Sjögren's syndrome, BTK inhibition reduced B cell activation, autoantibody production, and lymphocytic infiltration of exocrine glands, leading to attenuation of systemic inflammatory features. In pemphigus models, BTK blockade interfered with autoreactive B cell responses and Fc receptor-mediated activation of myeloid cells, thereby reducing blister formation.[71] In allergic urticarial models, BTK inhibition suppressed FcεRI signaling in mast cells and basophils, resulting in decreased histamine release and rapid control of inflammatory symptoms. Similarly, in models of immune thrombocytopenia, BTK inhibitors prevented Fcγ receptor-mediated platelet clearance by macrophages. Collectively, these studies demonstrate that BTK inhibition can modulate both autoantibody generation and downstream effector mechanisms across multiple organ systems.

Clinical Studies of BTK Inhibition in Other Autoimmune Diseases

Sjögren's Syndrome

The strongest clinical evidence outside MS currently exists for Sjögren's syndrome (SJS). In phase II LOUiSSe trial,[49] remibrutinib significantly reduced systemic disease activity as measured by the ESSDAI score over 24 weeks compared with placebo. While patient-reported symptoms such as dryness and fatigue (ESSPRI) did not improve significantly, a trend toward improved salivary flow was observed. These data suggest that BTK inhibition effectively targets systemic, B cell-driven disease manifestations in SJS, although glandular dysfunction and subjective symptoms may be less responsive.

Pemphigus Vulgaris and Autoimmune Blistering Diseases

Rilzabrutinib showed promising results in an open-label phase II study, demonstrating rapid disease control and steroid-sparing effects.[72] However, these encouraging findings did not translate into phase III success.[73] In the PEGASUS trial, rilzabrutinib failed to meet its primary endpoint of sustained complete remission compared to placebo, despite good tolerability. This discrepancy highlights challenges related to endpoint selection, background corticosteroid use, and placebo responses in pemphigus trials, and emphasizes the difficulty of translating biological efficacy into regulatory success.

Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (CSU) represents one of the clearest success stories for BTK inhibition.[74] Remibrutinib demonstrated rapid and robust symptom control in phase II studies and subsequently met co-primary endpoints in phase II REMIX trials, leading to regulatory submissions and approvals in some regions.[48] Fenebrutinib has also shown clinical activity in CSU,[75] supporting a class effect mediated through inhibition of FcεRI-driven mast cell and basophil activation. In addition, rilzabrutinib was evaluated in the RILECSU Phase 2 randomized trial,[76] where it significantly reduced itch and urticaria activity scores (UAS7, ISS7) versus placebo over 12 weeks in moderate-to-severe CSU refractory to H1 antihistamines, with improvements evident by week 1 and an acceptable safety profile. These results establish BTK inhibition as a highly effective strategy in IgE- and mast cell-driven disease.

Immune Thrombocytopenia and Other Emerging Indications

In immune thrombocytopenia (ITP), rilzabrutinib has produced rapid and durable platelet responses in phase II studies, with an acceptable safety profile, leading to ongoing phase II development and regulatory submissions. Beyond these indications, BTK inhibitors are being explored in a wide range of autoimmune and inflammatory diseases, including systemic sclerosis,[77] myasthenia gravis,[78] IgG4-related disease,[79] atopic dermatitis, and asthma.[80] Most of these programs remain in early clinical stages but illustrate the broad relevance of BTK-dependent pathways.

Summary

Clinical experience across multiple autoimmune diseases highlights both the promise and the limitations of BTK inhibition in the generalized therapy of autoimmune diseases. In primary Sjögren's syndrome, remibrutinib demonstrates that BTK inhibition can meaningfully reduce systemic disease activity, although symptomatic improvement remains challenging. Pemphigus illustrates how strong biological rationale and early efficacy may still fail in late-stage trials due to disease complexity and trial design. In contrast, chronic spontaneous urticaria and immune thrombocytopenia represent clear translational successes, where BTK inhibition directly targets dominant pathogenic mechanisms. Together, these indications emphasize that clinical impact of BTK inhibitors is highly disease-context dependent and strongest in conditions driven by Fc receptor-mediated effector pathways.

Targeting Approaches Beyond Small-Molecule Inhibitors

While the interference with BTK using small-molecule inhibitors (SMI) has been proven to successfully disrupt disease-driving activities of the enzyme, SMIs possess some drawbacks that can be countered using different approaches. These limitations can be for example drug selectivity, the development of therapy resistances or simply lie with the protein itself, as many targets might be undruggable with SMIs[81] (eg. proteins with no enzymatic activity such as structural proteins, transcription factors etc). Especially the emergence of C481 mutations in patients receiving long-term BTK

inhibitors has proven a challenge, with more than 50% of patients becoming insensitive to irreversible BTK inhibitors.[82] One novel approach to target BTK that tries to circumvent some of these limitations is the use of Proteolysis-Targeting Chimeras (PROTACs). This strategy is often based on already developed structures known to interact with a target protein, eg. based upon SMIs. The designed molecules then hijack the cells' own ubiquitin-proteasome system to degrade a protein-of-interest. Therefore, structurally, these molecules feature a target-protein binding site, a variable linker and a binding site for the E3 ubiquitin ligase. Interaction with the target protein will lead to the recruitment of the E3-ligase and the ubiquitination of the target, marking it for proteasomal degradation. Importantly, the PROTAC itself is not degraded during this process but remains available to mark another target protein for destruction.

L18I

L18I is a recently developed, BTK-targeting PROTAC that demonstrated an efficient destruction of BTK in vitro as well as in vivo in various organs.[83] Upon the induction of BTK or TLR signaling pathways, L18I treatment was associated with a reduced expression of the activation markers CD25, CD69 and CD86. In contrast, treatment with the ITK-family inhibitor ibrutinib only affected the expression of activation markers upon BTK receptor stimulation but did not affect TLR4-induced cellular activation. When tested in an animal model for SLE, L18I treatment reduced the induction of overall IgM and IgG as well as anti-nuclear antibodies. One severe complication in SLE is diffuse alveolar hemorrhage (DAH), in which patients present dyspnea as well as pulmonary infiltrates. In this context, both B cells as well as myeloid-derived monocytes and macrophages participate in the progression of DAH. Therefore, L18I was tested in a pristane-induced DAH model, reporting a drastic reduction in DAH prevalence, severity and immune cell infiltration into the lungs, an effect that was notably stronger than a treatment with ibrutinib. Overall, this also translated into improved survival for the animals treated with the BTK-targeting PROTAC. This early work highlights that BTK is not only targetable by SMIs but also by this novel concept of guiding proteins towards internal destruction complexes. However, if this translates into improved therapy regimens by either increased effectiveness or improved safety measures, still needs to be assessed in clinical and pre-clinical trials.

NX-5948

Another approach to facilitate protein inactivity is the use of molecular glues (MGs). These small molecules are designed to facilitate protein-protein interactions often by altering the surface conformation and thereby allowing novel interactions between normally non-interacting proteins. Through these interactions, MGs can alter the target protein's localization, stability or function. One specific sub form of MGs is molecular glue degraders, which alter the surface conformation of an E3 ligase receptor, thereby promoting proteins for degradation in a similar although more direct manner than PROTACs.[84] In comparison to SMIs, MGs offer advantages such as improved bioavailability, cell permeability and a lowered molecular weight. For the targeting of BTK, one molecular glue degrader has been described to date: NX-5948, which is currently explored in Phase 1 studies for the therapy of B cell malignancies.[85]

NX-2127

In a similar manner, NX-2127 acts as an MG to degrade BTK. Importantly, NX-2127 does not only bind wild type BTK but can also facilitate the destruction of C481-mutant variants, offering an alternative approach to patients with acquired resistance to BTK inhibitors.[86] In first clinical trials in patients with B cell malignancies, NX-2127 led to a substantial and lasting reduction in BTK protein expression regardless of initial BTK expression status.[87,88]

So far, these studies on PROTACs as well as molecular glues are focused on B cell-driven malignancies. But if the continued efforts demonstrate superiority of these approaches regarding efficacy or safety, their positioning might be broadened to also include autoimmune diseases.

Challenges, Future Directions and Concluding Remarks

Up-to-date, BTK inhibitors have been widely tested in a variety of autoimmune conditions. The results of these pre-clinical and clinical trials are relatively heterogeneous, which may relate to several independent and/or interdependent factors; first, many of the diseases in which BTK inhibitors have been trialed are still poorly understood themselves and accordingly,

disease-driving mechanisms and their relative clinical importance remain to be defined. For instance, B cell-driven mechanisms are considered central in multiple sclerosis and systemic lupus erythematosus, while Fc receptor-mediated activation of myeloid cells and mast cells may play a dominant role in immune thrombocytopenia and chronic spontaneous urticaria. This may explain why individual BTK inhibitors demonstrate limited efficacy in some indications, but show strong clinical benefit in others, particularly in IgE- and Fc receptor-driven diseases. Secondly, and related to the point of pathophysiological differences between the trialed conditions, many of these diseases furthermore contain a population of rather heterogenous patients. These two factors constitute a major challenge to predict overall efficacy of BTK inhibitors in a specific autoimmune condition. Third, in many of these conditions a broad immunosuppressive armamentarium of therapeutics exists so that clinical trials had to be designed to reveal superior efficacy, which in many cases cannot be easily achieved. Fourth, BTK inhibitors are still considered as one class of drugs, while clinical results using distinct BTK inhibitors in one immune condition apparently greatly vary, which is challenging to interpret and to communicate to the broader clinical field. For instance, in MS, fenebrutinib showed excellent control of de novo CNS lesion formation and relapse activity, while tolebrutinib rather revealed a selective effect in slowing down MS progression independent of its effect on relapse biology. In perspective, these differences may further relate to different abilities of the compounds to cross physiological barriers between compartments, such as the blood brain barrier, which is considered a prerequirement for a drug to successfully counteract MS progression. Besides determining efficacy, pharmacological differences between BTKis, such as covalent (irreversible) vs. non-covalent (reversible) binding, CNS-penetrant vs. peripherally restricted agents, may determine that over time, each individual BTKi used in a distinct condition may develop an individual safety profile, which cannot be extracted from the pharmacological mechanism of action alone.

As a result of the pre-clinical and clinical endeavors listed in this review (Table 1), our pathophysiological understanding of the respective underlying condition increased, especially in regard to its dependence on the BTK pathway. In this regard, future testing of highly effective BTK degraders will show to which extent this mechanism is central in disease development and progression of each individual disease, and accordingly whether and to what extent complete abrogation of BTK signaling can be exploited as a future therapeutic approach in autoimmunity.

Consent for Publication

All authors have read and agreed to the published version of the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This paper was not funded.

Disclosure

ST has received travel support from EMD Serono, speaker honoraria from Novartis and research support from the Universitätsmedizin Göttingen (Startförderung) and via the BOOST funding scheme (MDC Berlin). MSW receives research support from the National Multiple Sclerosis Society (NMSS; PP 1660), the Deutsche Forschungsgemeinschaft (DFG; WE 3547/5-1, TRR 274), from Novartis, TEVA, Biogen-Idec, Roche, Merck and the ProFutura Programm of the Universitätsmedizin Göttingen. The authors report no other conflicts of interest in this work.

References

1. Maas A, Hendriks RW. Role of Bruton's tyrosine kinase in B cell development. *Dev Immunol*. 2001;8(3–4):171–181. doi:10.1155/2001/28962
2. Wen T, Wang J, Shi Y, Qian H, Liu P. Inhibitors targeting Bruton's tyrosine kinase in cancers: drug development advances. *Leukemia*. 2021;35 (2):312–332. doi:10.1038/s41375-020-01072-6

3. Torke S, Weber MS. Inhibition of Bruton s tyrosine kinase as a novel therapeutic approach in multiple sclerosis. *Expert Opin Investig Drugs*. 2020;29(10):1143–1150. doi:10.1080/13543784.2020.1807934
4. De Bondt M, Renders J, Struyf S, Hellings N. Inhibitors of Bruton's tyrosine kinase as emerging therapeutic strategy in autoimmune diseases. *Autoimmun Rev*. 2024;23(5):103532. doi:10.1016/j.autrev.2024.103532
5. Zain R, Vihinen M. Structure-Function relationships of covalent and non-covalent BTK inhibitors. *Front Immunol*. 2021;12:694853. doi:10.3389/fimmu.2021.694853
6. Shirley M. Bruton tyrosine kinase inhibitors in B-Cell malignancies: their use and differential features. *Target Oncol*. 2022;17(1):69–84. doi:10.1007/s11523-021-00857-8
7. Tichenor MS, Wiener JJM, Rao NL, et al. Discovery of a potent and selective covalent inhibitor of Bruton's tyrosine kinase with oral anti-inflammatory activity. *ACS Med Chem Lett*. 2021;12(5):782–790. doi:10.1021/acsmedchemlett.1c00044
8. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014;370(24):2286–2294. doi:10.1056/NEJMoa1400029
9. Woyach JA, Ruppert AS, Guinn D, et al. BTK(C481S)-Mediated resistance to ibrutinib in chronic lymphocytic leukemia. *J Clin Oncol*. 2017;35(13):1437–1443. doi:10.1200/JCO.2016.70.2282
10. Wang H, Guo H, Yang J, et al. Bruton tyrosine kinase inhibitors in B-cell lymphoma: beyond the antitumour effect. *Exp Hematol Oncol*. 2022;11(1):60. doi:10.1186/s40164-022-00315-9
11. Toenjes ST, Heydari BS, Albright ST, et al. Controlling Ibrutinib's conformations about its heterobiaryl axis to increase BTK selectivity. *ACS Med Chem Lett*. 2023;14(3):305–311. doi:10.1021/acsmedchemlett.2c00523
12. Media Update: Patient enrollment of phase III tolebrutinib trials paused in the U.S. 2022;2022.
13. FDA puts partial hold on trials of Merck KGaA's evobrutinib in MS. 2023;2023.
14. Oh J, Arnold DL, Cree BAC, et al. Tolebrutinib versus teriflunomide in relapsing multiple sclerosis. *N Engl J Med*. 2025;392(19):1893–1904. doi:10.1056/NEJMoa2415985
15. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. *Mol Cancer*. 2018;17(1):57. doi:10.1186/s12943-018-0779-z
16. Duhren-von Minden M, Ubelhart R, Schneider D, et al. Chronic lymphocytic leukaemia is driven by antigen-independent cell-autonomous signalling. *Nature*. 2012;489(7415):309–312. doi:10.1038/nature11309
17. Palma M, Mulder TA, Osterborg A. BTK inhibitors in chronic lymphocytic leukemia: biological activity and immune effects. *Front Immunol*. 2021;12:686768. doi:10.3389/fimmu.2021.686768
18. Cinar M, Hamedani F, Mo Z, Cinar B, Amin HM, Alkan S. Bruton tyrosine kinase is commonly overexpressed in mantle cell lymphoma and its attenuation by Ibrutinib induces apoptosis. *Leuk Res*. 2013;37(10):1271–1277. doi:10.1016/j.leukres.2013.07.028
19. Chang BY, Francesco M, De Rooij MF, et al. Egress of CD19(+)CD5(+) cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor ibrutinib in mantle cell lymphoma patients. *Blood*. 2013;122(14):2412–2424. doi:10.1182/blood-2013-02-482125
20. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. *N Engl J Med*. 2012;367(9):826–833. doi:10.1056/NEJMoa1200710
21. Buske C, Jurczak W, Salem JE, Dimopoulos MA. Managing Waldenstrom's macroglobulinemia with BTK inhibitors. *Leukemia*. 2023;37(1):35–46. doi:10.1038/s41375-022-01732-9
22. Guerrera ML, Tsakmaklis N, Xu L, et al. MYD88 mutated and wild-type Waldenstrom's Macroglobulinemia: characterization of chromosome 6q gene losses and their mutual exclusivity with mutations in CXCR4. *Haematologica*. 2018;103(9):e408–e411. doi:10.3324/haematol.2018.190181
23. Bendicksen L, King L, Cliff ERS, Kesselheim AS. Discovering a transformative cancer drug: the case of ibrutinib. *Drug Discov Today*. 2025;30(12):104542. doi:10.1016/j.drudis.2025.104542
24. Lassmann H. Multiple Sclerosis Pathology. *Cold Spring Harb Perspect Med*. 2018;8(3):a028936. doi:10.1101/cshperspect.a028936
25. Reich DS, Lucchinetti CF, Calabresi PA. Multiple Sclerosis. *N Engl J Med*. 2018;378(2):169–180. doi:10.1056/NEJMra1401483
26. Frischer JM, Bramow S, Dal-Bianco A, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. *Brain*. 2009;132(Pt 5):1175–1189. doi:10.1093/brain/awp070
27. Lassmann H, van Horssen J, Mahad D. Progressive multiple sclerosis: pathology and pathogenesis. *Nat Rev Neurol*. 2012;8(11):647–656. doi:10.1038/nrneurol.2012.168
28. Hauser SL, Cree BAC. Treatment of multiple sclerosis: a review. *Am J Med*. 2020;133(12):1380–1390e2. doi:10.1016/j.amjmed.2020.05.049
29. Cree BAC, Hollenbach JA, Bove R, et al; University of California SFMSET. Silent progression in disease activity-free relapsing multiple sclerosis. *Ann Neurol*. 2019;85(5):653–666. doi:10.1002/ana.25463
30. Prinz M, Priller J. Microglia and brain macrophages in the molecular age: from origin to neuropsychiatric disease. *Nat Rev Neurosci*. 2014;15(5):300–312. doi:10.1038/nrn3722
31. Voet S, Prinz M, van Loo G. Microglia in central nervous system inflammation and multiple sclerosis pathology. *Trends Mol Med*. 2019;25(2):112–123. doi:10.1016/j.molmed.2018.11.005
32. Bassani C, Molinari M, Romeo V, et al. The contribution of BTK signaling in myeloid cells to neuroinflammation. *Front Immunol*. 2025;16:1595069. doi:10.3389/fimmu.2025.1595069
33. Kramer J, Bar-Or A, Turner TJ, Wiendl H. Bruton tyrosine kinase inhibitors for multiple sclerosis. *Nat Rev Neurol*. 2023;19(5):289–304. doi:10.1038/s41582-023-00800-7
34. Li C, Morch MT, Gorter R, et al. Bruton tyrosine kinase in lesions of multiple sclerosis and 3 of its models. *Neurol Neuroimmunol Neuroinflamm*. 2025;12(4):e200413. doi:10.1212/NXI.0000000000200413
35. Menzfeld C, John M, Van Rossum D, et al. Tyrphostin AG126 exerts neuroprotection in CNS inflammation by a dual mechanism. *Glia*. 2015;63(6):1083–1099. doi:10.1002/glia.22803
36. Evonuk KS, Wang S, Mattie J, et al. Bruton's tyrosine kinase inhibition reduces disease severity in a model of secondary progressive autoimmune demyelination. *Acta Neuropathol Commun*. 2023;11(1):115. doi:10.1186/s40478-023-01614-w
37. Torke S, Pretzsch R, Hausler D, et al. Inhibition of Bruton's tyrosine kinase interferes with pathogenic B-cell development in inflammatory CNS demyelinating disease. *Acta Neuropathol*. 2020;140(4):535–548. doi:10.1007/s00401-020-02204-z

38. Dybowski S, Thode J, Freier M, et al. Bruton tyrosine kinase inhibition limits multiple sclerosis disease-driving inflammation while promoting regulatory B cells. *Neurol Neuroimmunol Neuroinflamm*. 2026;13(1):e200510. doi:10.1212/NXI.0000000000200510
39. Geladaris A, Torke S, Saberi D, et al. BTK inhibition limits microglia-perpetuated CNS inflammation and promotes myelin repair. *Acta Neuropathol*. 2024;147(1):75. doi:10.1007/s00401-024-02730-0
40. Gruber RC, Wirak GS, Blazier AS, et al. BTK regulates microglial function and neuroinflammation in human stem cell models and mouse models of multiple sclerosis. *Nat Commun*. 2024;15(1):10116. doi:10.1038/s41467-024-54430-8
41. Montalban X, Arnold DL, Weber MS, et al. Placebo-Controlled trial of an oral BTK inhibitor in multiple sclerosis. *N Engl J Med*. 2019;380 (25):2406–2417. doi:10.1056/NEJMoa1901981
42. Montalban X, Vermersch P, Arnold DL, et al. Safety and efficacy of evobrutinib in relapsing multiple sclerosis (evolutionRMS1 and evolutionRMS2): two multicentre, randomised, double-blind, active-controlled, Phase 3 trials. *Lancet Neurol*. 2024;23(11):1119–1132. doi:10.1016/S1474-4422(24)00328-4
43. Reich DS, Arnold DL, Vermersch P, et al. Safety and efficacy of tolebrutinib, an oral brain-penetrant BTK inhibitor, in relapsing multiple sclerosis: a phase 2b, randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2021;20(9):729–738. doi:10.1016/S1474-4422(21)00237-4
44. Fox RJ, Bar-Or A, Traboulsee A, et al. Tolebrutinib in nonrelapsing secondary progressive multiple sclerosis. *N Engl J Med*. 2025;392 (19):1883–1892. doi:10.1056/NEJMoa2415988
45. Bar-Or A, Dufek M, Budincevic H, et al. Safety and efficacy of fenebrutinib in relapsing multiple sclerosis (FENopta): a multicentre, double-blind, randomised, placebo-controlled, phase 2 trial and open-label extension study. *Lancet Neurol*. 2025;24(8):656–666. doi:10.1016/S1474-4422(25) 00174-7
46. Genentech's fenebrutinib shows unprecedented positive phase III results as the potential first and only BTK inhibitor in both relapsing and primary progressive multiple sclerosis. 2025. Available from: https://www.gene.com/media/press-releases/15089/2025-11-09/genentechs-fenebrutinib-shows-unpreceden. Accessed July 03, 2026.
47. Genentech's fenebrutinib maintains near-complete suppression of disease activity and disability progression for up to two years in people with relapsing multiple sclerosis. 2025. Available from: https://www.gene.com/media/press-releases/15064/2025-05-29/genentechs-fenebrutinib-maintains-near-c. Accessed July 03, 2026.
48. Metz M, Gimenez-Arnau A, Hide M, et al. Remibrutinib in chronic spontaneous urticaria. *N Engl J Med*. 2025;392(10):984–994. doi:10.1056/NEJMoa2408792
49. Dorner T, Kaul M, Szanto A, et al. Efficacy and safety of remibrutinib, a selective potent oral BTK inhibitor, in Sjogren's syndrome: results from a randomised, double-blind, placebo-controlled phase 2 trial. *Ann Rheum Dis*. 2024;83(3):360–371. doi:10.1136/ard-2023-224691
50. Xu Y, Tang W. Positive Phase 2 Results of Orelabrutinib in Patients with Relapsing-Remitting Multiple Sclerosis. In: *Presented At: 2025 ACTRIMS Forum*. West Palm Beach, FL: 094
51. InnoCare announces end-of-phase 2 meeting with FDA and agreement to initiate a phase III clinical trial of orelabrutinib for the treatment of PPMS. *News Release InnoCare*. 2024.
52. Chang BY, Huang MM, Francesco M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 ameliorates autoimmune arthritis by inhibition of multiple effector cells. *Arthritis Res Ther*. 2011;13(4):R115. doi:10.1186/ar3400
53. Nyhoff LE, Barron BL, Johnson EM, et al. Bruton's tyrosine kinase deficiency inhibits autoimmune arthritis in mice but fails to block immune complex-mediated inflammatory arthritis. *Arthritis Rheumatol*. 2016;68(8):1856–1868. doi:10.1002/art.39657
54. Zhang Z, Tan M, Xie Z, Dai L, Chen Y, Zhao Y. Identification of lysine succinylation as a new post-translational modification. *Nat Chem Biol*. 2011;7(1):58–63. doi:10.1038/nchembio.495
55. Hartkamp LM, Fine JS, van Es IE, et al. Btk inhibition suppresses agonist-induced human macrophage activation and inflammatory gene expression in RA synovial tissue explants. *Ann Rheum Dis*. 2015;74(8):1603–1611. doi:10.1136/annrheumdis-2013-204143
56. Park JK, Byun JY, Park JA, et al. HM71224, a novel Bruton's tyrosine kinase inhibitor, suppresses B cell and monocyte activation and ameliorates arthritis in a mouse model: a potential drug for rheumatoid arthritis. *Arthritis Res Ther*. 2016;18:91. doi:10.1186/s13075-016-0988-z
57. Chan P, Yu J, Chinn L, et al. Population pharmacokinetics, efficacy exposure-response analysis, and model-based meta-analysis of fenebrutinib in subjects with rheumatoid arthritis. *Pharm Res*. 2020;37(2):25. doi:10.1007/s11095-019-2752-y
58. Cohen S, Tuckwell K, Katsumoto TR, et al. Fenebrutinib versus placebo or adalimumab in rheumatoid arthritis: a randomized, double-blind, phase ii trial (Andes Study). *Arthritis Rheumatol*. 2020;72(9):1435–1446. doi:10.1002/art.41275
59. Peterfy CBM, Choy E, Schett G, et al. A phase IIb, randomized, double-blind study in patients with rheumatoid arthritis evaluating the safety and efficacy of evobrutinib compared with placebo in patients with an inadequate response to methotrexate. *Arthritis Rheumatol*. 2020;72(10).
60. Genovese MC, Spindler A, Sagawa A, et al. Safety and efficacy of poseltinib, bruton's tyrosine kinase inhibitor, in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled, 2-part Phase II Study. *J Rheumatol*. 2021;48(7):969–976. doi:10.3899/jrheum.200893
61. Mease P, Strand V, Shalamberidze L, et al. A Phase II, double-blind, randomised, placebo-controlled study of BMS945429 (ALD518) in patients with rheumatoid arthritis with an inadequate response to methotrexate. *Ann Rheum Dis*. 2012;71(7):1183–1189. doi:10.1136/annrheumdis-2011-200704
62. Du Y, Lei L, Ding H, et al. Targeting multiple end organs in lupus and other systemic rheumatic diseases by inhibiting bruton's tyrosine kinase. *Front Immunol*. 2022;13:893899. doi:10.3389/fimmu.2022.893899
63. Lorenzo-Vizcaya A, Fasano S, Isenberg DA. Bruton's Tyrosine Kinase inhibitors: a new therapeutic target for the treatment of SLE? *Immunotargets Ther*. 2020;9:105–110. doi:10.2147/ITT.S240874
64. Ringheim GE, Wampole M, Oberoi K. Bruton's Tyrosine Kinase (BTK) inhibitors and autoimmune diseases: making sense of BTK inhibitor specificity profiles and recent clinical trial successes and failures. *Front Immunol*. 2021;12:662223. doi:10.3389/fimmu.2021.662223
65. Satterthwaite AB. Bruton's Tyrosine kinase, a component of B cell signaling pathways, has multiple roles in the pathogenesis of lupus. *Front Immunol*. 2017;8:1986. doi:10.3389/fimmu.2017.01986
66. Rozkiewicz D, Hermanowicz JM, Kwiatkowska I, Krupa A, Pawlak D. Bruton's Tyrosine Kinase inhibitors (BTKIs): review of preclinical studies and evaluation of clinical trials. *Molecules*. 2023;28(5):2400. doi:10.3390/molecules28052400
67. Isenberg D, Furie R, Jones NS, et al. Efficacy, Safety, and pharmacodynamic effects of the Bruton's Tyrosine Kinase Inhibitor Fenebrutinib (GDC-0853) in systemic lupus erythematosus: results of a phase II, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol*. 2021;73 (10):1835–1846. doi:10.1002/art.41811

68. Wallace DJ, Dorner T, Pisetsky DS, et al. Efficacy and safety of the Bruton's Tyrosine Kinase inhibitor evobrutinib in systemic lupus erythematosus: results of a phase II, randomized, double-blind, placebo-controlled dose-ranging trial. *ACR Open Rheumatol*. 2023;5(1):38–48. doi:10.1002/acr2.11511
69. Li R, Zhu X, Liu S, et al. LB0005 ORELABRUTINIB, AN irreversible inhibitor of Bruton's Tyrosine Kinase (BTK), for the treatment of Systemic Lupus Erythematosus (SLE): results of a randomized,double-blind,placebo-controlled,phase IB/IIA dose-finding study. *Ann Rheumatic Dis*. 2022;81(1):210. doi:10.1136/annrheumdis-2022-eular.5086a
70. InnoCare's BTK inhibitor advances to Phase III in SLE. 2025. Available from: https://www.clinicaltrialsarena.com/news/innocare-orelabrutinib-btk-inhibitor-sle-phase-iib-results/. Accessed July 03, 2026.
71. Langrish CL, Bradshaw JM, Francesco MR, et al. Preclinical efficacy and anti-inflammatory mechanisms of action of the Bruton Tyrosine Kinase inhibitor rilzabrutinib for immune-mediated disease. *J Immunol*. 2021;206(7):1454–1468. doi:10.4049/jimmunol.2001130
72. Murrell DF, Patsatsi A, Stavropoulos P, et al. Proof of concept for the clinical effects of oral rilzabrutinib, the first Bruton tyrosine kinase inhibitor for pemphigus vulgaris: the phase II BELIEVE study. *Br J Dermatol*. 2021;185(4):745–755. doi:10.1111/bjd.20431
73. Murrell DF, Caux F, Patsatsi A, et al. Efficacy and safety of rilzabrutinib in pemphigus: PEGASUS Phase 3 Randomized Study. *J Invest Dermatol*. 2024;144(8):1762–1771e6. doi:10.1016/j.jid.2024.02.023
74. Maurer M, Berger W, Gimenez-Arnau A, et al. Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2022;150(6):1498–1506e2. doi:10.1016/j.jaci.2022.08.027
75. Metz M, Sussman G, Gagnon R, et al. Fenebrutinib in H(1) antihistamine-refractory chronic spontaneous urticaria: a randomized phase 2 trial. *Nat Med*. 2021;27(11):1961–1969. doi:10.1038/s41591-021-01537-w
76. Gimenez-Arnau A, Ferrucci S, Ben-Shoshan M, et al. Rilzabrutinib in antihistamine-refractory chronic spontaneous urticaria: the RILECSU phase 2 randomized clinical trial. *JAMA Dermatol*. 2025;161(7):679–687. doi:10.1001/jamadermatol.2025.0733
77. Ando T, Oda H. Bruton tyrosine kinase inhibition in systemic sclerosis: a promising new B-cell therapy. *Br J Dermatol*. 2025;193(3):358–359. doi:10.1093/bjd/ljaf202
78. Tavakoli GM, Yazdanpanah N, Rezaei N. Targeting Bruton's tyrosine kinase (BTK) as a signaling pathway in immune-mediated diseases: from molecular mechanisms to leading treatments. *Adv Rheumatol*. 2024;64(1):61. doi:10.1186/s42358-024-00401-y
79. Tanaka Y, Stone JH. Perspectives on current and emerging therapies for immunoglobulin G4-related disease. *Mod Rheumatol*. 2023;33(2):229–236. doi:10.1093/mr/roac141
80. Lin EV, Suresh RV, Dispenza MC. Bruton's tyrosine kinase inhibition for the treatment of allergic disorders. *Ann Allergy Asthma Immunol*. 2024;133(1):33–42. doi:10.1016/j.anai.2024.03.002
81. Martin-Acosta P, Xiao X. PROTACs to address the challenges facing small molecule inhibitors. *Eur J Med Chem*. 2021;210:112993. doi:10.1016/j.ejmech.2020.112993
82. Naeem A, Utro F, Wang Q, et al. Pirtobrutinib targets BTK C481S in ibrutinib-resistant CLL but second-site BTK mutations lead to resistance. *Blood Adv*. 2023;7(9):1929–1943. doi:10.1182/bloodadvances.2022008447
83. Zhu C, Yang Z, Zhang Y, et al. PROTAC for Bruton's tyrosine kinase degradation alleviates inflammation in autoimmune diseases. *Cell Discov*. 2024;10(1):82. doi:10.1038/s41421-024-00711-x
84. Tomlinson ACA, Knox JE, Brunsveld L, Ottmann C, Yano JK. The "three body solution": structural insights into molecular glues. *Curr Opin Struct Biol*. 2025;91:103007. doi:10.1016/j.sbi.2025.103007
85. Li N, Sheng J, Zhu HH. Breakthroughs in treatment for hematological malignancies: latest updates on molecular glue, PROTACs and RNA degraders from ASH 2024. *J Hematol Oncol*. 2025;18(1):26. doi:10.1186/s13045-025-01674-6
86. Robbins DW, Noviski MA, Tan YS, et al. Discovery and preclinical pharmacology of NX-2127, an orally bioavailable degrader of Bruton's Tyrosine Kinase with immunomodulatory activity for the treatment of patients with B cell malignancies. *J Med Chem*. 2024;67(4):2321–2336. doi:10.1021/acs.jmedchem.3c01007
87. Salvaris RT, Brennan J, Lewis KL. BTK is the target that keeps on giving: a review of BTK-Degrader drug development, clinical data, and future directions in CLL. *Cancers*. 2025;17(3):557. doi:10.3390/cancers17030557
88. Danilov AT, Patel MT, Wierda K, et al. A First-In-Human phase 1 trial of NX-2127, a first-in-class Bruton's Tyrosine Kinase (BTK) dual-targeted protein degrader with immunomodulatory activity, in patients with relapsed/refractory B cell malignancies. Presented At: 626Aggressive lymphomas: prospective therapeutic trials. 2023.