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EDITED BY

Guoliang Meng,
Nantong University, China

REVIEWED BY

Zhongwang Wang,
Sichuan University, China
Baonian Liu,
Shanghai University of Traditional Chinese
Medicine, China

*CORRESPONDENCE

Zhifei Xu,
✉ xzfzjut@zju.edu.cn
Peihua Luo,
✉ peihualuo@zju.edu.cn

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Advancements in research on the cardiovascular toxicity caused by TEC family kinases inhibitors

Yi Zhang¹, Huangxi Fu¹, Xingchen Kang¹, Zixuan Qiu¹, Hao Yan¹,
Qiaojun He^{1,2,3}, Bo Yang^{2,3,4}, Zhifei Xu^{1*} and Peihua Luo^{1,2*}

¹Center for Drug Safety Evaluation and Research of Zhejiang University, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, Zhejiang, China, ²Innovation Institute for Artificial Intelligence in Medicine of Zhejiang University, Hangzhou, Zhejiang, China, ³School of Medicine, Hangzhou City University, Hangzhou, China, ⁴Institute of Pharmacology and Toxicology, Zhejiang Key Laboratory of Anti-Cancer Drug Research, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, China

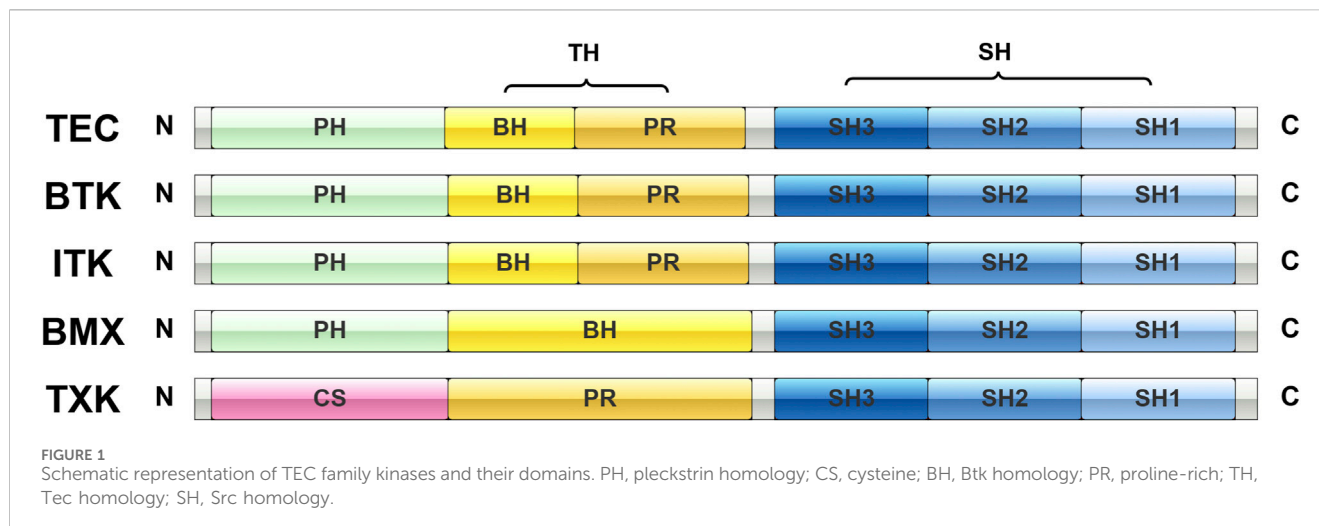
The tyrosine kinase expressed in hepatocellular carcinoma (TEC) family kinases (TFKs) are a subfamily of non-receptor protein tyrosine kinases (PTKs) that include five members: TEC, bruton's tyrosine kinase (BTK), interleukin 2-inducible T-cell kinase (ITK/EMT/TSK), bone marrow tyrosine kinase on chromosome X (BMX/ETK), and tyrosine-protein kinase (TXK/RLK). They play key roles in cell signaling and immune regulation. Emerging evidence highlights their involvement in cardiovascular diseases (CVDs) such as ischemic heart disease (IHD), atherosclerosis (AS), sepsis-related dysfunction, atrial fibrillation (AF), myocardial hypertrophy, coronary atherosclerotic heart disease, myocardial infarction (MI), and post-myocardial infarction complications. However, no review has comprehensively addressed the cardiovascular toxicity of TFKs inhibitors. This review provides a comprehensive and systematic analysis of the cardiovascular toxicity profiles of TFK inhibitors (TFKis), focusing on underlying molecular mechanisms, comparing toxicity across different agents and generations, and discussing clinical implications.

KEYWORDS

bruton's tyrosine kinase, cardiovascular toxicity, clinical safety, inhibitors, TEC family kinases

1 Introduction

Protein kinases catalyze the phosphorylation of proteins, altering their activity or their ability to interact with other molecules, thereby affecting cellular growth, differentiation, survival, and proliferation. Additionally, kinases play a role in numerous signal transduction cascades. Thus, the dysregulation of protein kinase activity is pivotal in the pathogenesis of numerous diseases, encompassing autoimmune, cardiovascular, neurological, and inflammatory disorders, as well as a spectrum of cancers (Das and Hong, 2020). TEC family kinases (TFKs), a subgroup of the non-receptor tyrosine kinases (NRTKs), constitute the second-largest family of cytoplasmic tyrosine kinases in humans. Receptor-mediated signaling is known to be highly complex, guiding many parallel processes such as proliferation, programmed cell death, differentiation, migration, and secretion. Together, these processes underpin complex and essential behaviors of the organism (Yu and Smith, 2011). Therefore, TFKs play significant roles in various cellular processes, including immune responses, cell survival, and signaling pathways involved in cancer, inflammation, and



CVDs (Yin et al., 2022). TFKs, such as TEC, BTK, and ITK, have been identified as therapeutic targets of autoimmune disorders and cancers (Yin et al., 2022).

However, the clinical use of TFK inhibitors (TFKis), particularly Bruton's tyrosine kinase inhibitors (BTKis), has revealed significant cardiovascular adverse effects, such as AF, hypertension, and heart failure (HF). Although several reviews have focused on BTKi cardiotoxicity, a comprehensive synthesis encompassing all TFK members (BTK, TEC, ITK, BMX, TXK) is lacking. This review aims to fill this gap by systematically examining the cardiovascular toxicity profiles, mechanistic insights, and clinical management strategies associated with TFKis, thereby providing a holistic perspective to inform clinical practice and future drug development.

2 Overview of TEC family kinases and their inhibitors

2.1 TEC family kinases members

TEC family kinases (TFKs), the second largest subfamily of the NRTKs, consist of five members, including TEC, BTK, ITK/EMT/TSK, RLK/TXK and BMX/ETK (Siveen et al., 2018). TEC was initially identified in liver cancer cells and is widely expressed in hematopoietic cells, playing a crucial role in immune cell signaling. TEC is involved in regulating the activation of various immune cells, including T cells and B cells (Lucas et al., 2003; Yin et al., 2022). BTK is a well-known TFK critical for B cell development and signaling. Mutations in BTK result in X-linked agammaglobulinemia (XLA), a condition characterized by a severe deficiency in B cell function and immunodeficiency (Marron et al., 2012). ITK is primarily expressed in T cells and plays a vital role in T cell receptor signaling, affecting T cell activation, differentiation, and immune response (Lechner et al., 2020). Like other TFK, TXK is involved in immune cell signaling, specifically within the T cell lineage. BMX is a TFK implicated in hematopoiesis and immune responses, especially within T cells and NK cells (Yin et al., 2022).

2.2 Structure and function of TEC family kinases

TFKs share a conserved C-terminal kinase domain and an N-terminal region lacking a transmembrane helix (Figure 1) (An and Zhang, 2024; Yang et al., 2001). At their amino terminus, all members of this family except TXK contain a pleckstrin homology (PH) domain. As PH domain can bind phosphoinositides, TFKs are assumed to act as the connection between phosphotyrosine-mediated and phospholipid-mediated signaling pathways; for BTK, this domain has been shown to bind inositol phosphates *in vitro* and to be responsible for membrane localization *in vivo* (An and Zhang, 2024). In TXK, the PH structural domain is replaced by a cysteine (Cys) module that facilitates membrane association through palmitoylation (An and Zhang, 2024). TFKs also share a TEC homology (TH) domain (An and Zhang, 2024; Yang et al., 2001) containing a series of zinc-binding BTK homology (BH) modules and proline-rich (PR) modules (An and Zhang, 2024). However, the TH domain of TXK lacks the BH module, while the TH domain of BMX lacks the PR module (An and Zhang, 2024). The TH domain is sequentially followed by the Src Homology 3 (SH3), Src Homology 2 (SH2), and Src Homology 1 (SH1) domains (Andersen et al., 2019; Yang et al., 2001).

The SH3 domain primarily facilitates protein-protein interactions and has been found to potentially play a role in the negative regulation of protein tyrosine kinase activity (Andersen et al., 2019). Studies on BTK, ITK, and TXK have shown that their autophosphorylation sites are located in the SH3 structural domain (An and Zhang, 2024). The SH2 domain is responsible for mediating interactions with phosphorylated tyrosine residues on other proteins, essential for signal transduction (An and Zhang, 2024). Kinase domain that mediates phosphorylation of downstream targets, typically involved in cellular signaling pathways. PH domain interacts with phosphoinositides and helps regulate the localization of the kinase within the cell (Yin et al., 2022). These domains allow TFKs to transduce signals in response to various stimuli, including antigen receptor engagement and cytokine signaling.

TABLE 1 Research status of BTK inhibitors launched in the market.

| Drug | Characteristic(s) | Disease(s) | R&D progress and R&D company | IC50 (nM) | | | | | References(s) |
|--------------------------------------|--|--|---|-----------|---------|-------|-------|-----|---|
| | | | | BTK | ITK | TEC | BMX | TXK | |
| Ibrutinib/ Imbruvica (PCI-32765) | First-in-class BTKi | Treated or untreated CLL/SLL (2014), WM (2015), cGVHD (2017) | Approved by FDA and EMA in 2013 Pharmacyclics/ Abbvie/Johnson and Johnson | 0.5 | 10.7 | 78 | 0.8 | 2 | Honigberg et al. (2010), Cameron and Sanford (2014), Schwarzbich and Witzens-Harig (2014) |
| Acalabrutinib/ Calquence (ACP-196) | Decreased off-target bindings Increased selectivity Improved safety profiles | Untreated or refractory CLL/SLL, pretreated MCL | Approved by FDA and EMA in 2017 AstraZeneca/ Acerta Pharma BV | 5.1 | >1,000 | 93 | 46 | 368 | Byrd et al. (2016), Acalabrutinib (2012), Markham and Dhillon (2018) |
| Zanubrutinib/ Brukinsa (BGB-3111) | Decreased off-targets with improved safety profiles Higher selectivity | CLL/SLL, untreated or pretreated MCL, previously treated or untreated WM | Approved by FDA, EMA and NMPA in 2019 BeiGene | 0.22 | 30 | 1.9 | 36 | 170 | Zanubrutinib (2012), Syed (2020) |
| Tirabrutinib/ Velebru® (GS/ONO-4059) | Decreased off-targets with increased selectivity | R/R PCNSL, treated or untreated WM, LPL | Approved by PMDA in 2020 (for use in Japan only) Ono Pharmaceutical | 6.8 | >20,000 | 48 | 6 | 92 | Dhillon (2020) |
| Orelabrutinib (ICP-022) | Reduces off-target effects with similar selectivity to Zanubrutinib Higher synergy with R-CHOP regimen than ibrutinib | Previously treated R/R MCL, CLL/SLL, R/R MZL, MS | Approved by NMPA in 2020 (for use in China only) Approved by FDA (BTD) in 2021 Innocare Pharma | 1.6 | NA | NA | NA | NA | Dhillon (2021), Zhang et al. (2020) |
| Pirtobrutinib (LOXO-305) | First-in-class noncovalent FDA-approved BTKi | Previously treated CLL/SLL, Previously treated R/R MCL | Approved by FDA in 2023 Eli Lilly and Company | 3.15 | >5,000 | 1,234 | 1,155 | 209 | Keam (2023) |

CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia; cGVHD, chronic; MCL, mantle cell lymphoma; R/R PCNSL, relapsed/refractory primary central nervous system lymphoma; LPL, lymphoplasmacytic lymphoma; R/R MZL, relapsed/refractory marginal zone lymphoma; MS, multiple sclerosis; NA, no data.

3 Mechanism of cardiovascular toxicity induced by TEC family inhibitors

3.1 BTK inhibitors (BTKis)

3.1.1 Ibrutinib (Imbruvica®)

Ibrutinib was the first BTKi approved by the FDA in 2013 (Table 1). It is an orally administered, effective, irreversible first-generation BTK inhibitor that covalently binds to a cysteine residue (Cys-481) near the ATP-binding pocket of BTK (Honigberg et al., 2010). As a result, it inhibits B cell receptor (BCR) signaling and downregulates nuclear factor kappa-B (NF- κ B) signaling, drastically decreasing tumor growth and boosting apoptosis in the process. Ibrutinib is used to treat chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström's macroglobulinemia (WM), marginal zone lymphoma (MZL), and graft-versus-host disease (GVHD) (Christensen et al., 2022; Honigberg et al., 2010).

In addition to BTK, ibrutinib inhibits other intracellular kinases, including B lymphoid tyrosine kinase (BLK), BMX, TEC, ITK, and Janus kinase 3 (JAK3) (Rozkiewicz et al., 2023). The advent of BTKi has generated a unique toxicity profile, driven by off-target inhibition of other kinases (Lipsky and Lamanna, 2020). With 11 years of data since the initial approval of ibrutinib, the toxicity profile of BTKi as a class is well established, including cardiac arrhythmias (CA), hypertension, bleeding, infections,

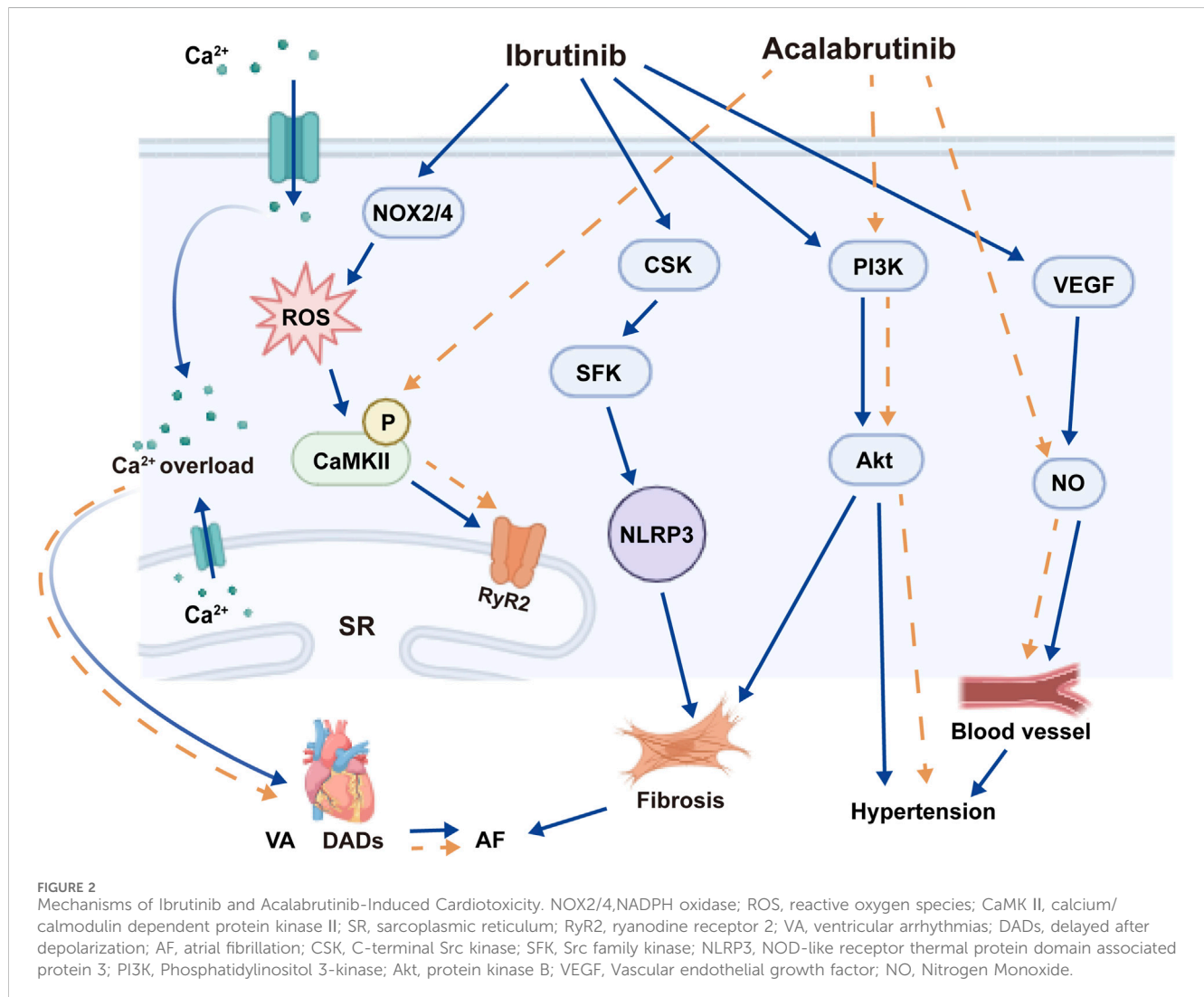
diarrhea, and arthralgias (Dickerson et al., 2019; Guha et al., 2018; Khountham et al., 2021; Mato et al., 2018; Wiczler et al., 2017). Adverse effects, rather than disease progression, are the most common reason for discontinuing ibrutinib, with cardiac side effects causing more than 10% of patients to discontinue treatment. Atrial fibrillation (AF) is the most common cause of drug discontinuation due to toxicity in patients taking ibrutinib, leading to cessation in 20%–60% of cases where it occurs (Maddocks et al., 2015; Wiczler et al., 2017). It occurs in 5%–16% of patients, most frequently in those older than 65 years of age and/or with cardiovascular risk factors (Pineda-Gayoso et al., 2020; Tam et al., 2020; Wiczler et al., 2017). Hypertension is the most common cardiac adverse event associated with ibrutinib, reported in up to 30% of patients in clinical trials and up to 80% in real-world studies (Dickerson et al., 2019). The summary of long-term follow-up data from several late-stage ibrutinib trials indicates that there may be an increased risk of heart failure. In these analyses, it was observed that up to 5% of patients developed heart failure, typically occurring several years after the initiation of treatment (Barr et al., 2022; Munir et al., 2019). A large retrospective analysis of 860 patients with CLL treated with ibrutinib revealed that, compared with chemotherapy, the risk of heart failure in patients treated with ibrutinib was 7.7% over 3 years (Table 2) (Abdel-Qadir et al., 2021).

Ibrutinib primarily increases the risk of AF through its off-target effect on the C-terminal Src kinase (CSK) (Xiao et al.,

TABLE 2 Cardiovascular toxicities associated with BTK inhibitors.

| Drug | Atrial Fibrillation | Ventricular Arrhythmias | Hypertension | Heart Failure |
|---------------|---------------------|-------------------------|--------------|---------------|
| Ibrutinib | +++ | ++ | +++ | + |
| Acalabrutinib | ++ | ++ | ++ | ? |
| Zanubrutinib | ++ | ? | ++ | ? |
| Pirtobrutinib | + | ? | ? | ? |

? Indicates areas where systematic cardiac data are not widely available.



2020). In a cardiomyocyte specific CSK knockout mouse model, Xiao et al. demonstrated increased rates of AF, left atrial enlargement, myocardial fibrosis, and inflammation with preserved ejection fraction (Xiao et al., 2020). Additionally, the CSK knockout mice exhibited a cytokine profile akin to that observed in mice treated with ibrutinib, along with a comparable gene expression pattern, suggesting similarities in the mechanisms underlying CSK loss and the use of ibrutinib. The connection between the inhibition of CSK and AF remains unclear, but it may be associated with downstream effects on the

NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome (Figure 2) (Awan et al., 2020). Long-term use of Ibrutinib can inhibit CSK from phosphorylating the carboxyl terminal of Src family kinases (SFK), which leads to the enhancement of SFK activity, atrial fibrosis, and activation of inflammatory reactions, thus increasing the susceptibility to AF (Figure 2). In addition to the CSK-mediated pathway, ibrutinib has also been demonstrated to elevate the expression of calmodulin kinase 2 (CaMK II) and enhance the phosphorylation of ryanodine receptor 2 (RyR 2) within the

cardiomyocyte endoplasmic reticulum (Figure 2). This process impairs intracellular calcium management and initiates ectopic electrical activity (Awan et al., 2020).

The mechanism by which ibrutinib induces hypertension is not well understood (Figure 2). One potential mechanism involves its effects on vascular endothelial growth factor (VEGF). Ibrutinib has been demonstrated to reduce the secretion of homeostatic chemokines Chemokine C-X-C motif ligand 12 (CXCL12), CXCL13, and C-C Motif Chemokine Ligand 19 (CCL19), as well as VEGF in human cell lines, leading to decreased nitric oxide production and increased vascular tone (Pandey et al., 2018; Ping et al., 2017). Vascular remodeling and the production of inflammatory cytokines, resulting from the downregulation of the PI3K pathway mediated by BTK and TEC, have also been proposed as potential mechanisms (Liu N. et al., 2013; McMullen et al., 2014).

Ibrutinib-induced ventricular arrhythmias (VAs) are likely mediated by acute dysregulation of cardiomyocyte calcium handling and repolarization dynamics (Figure 2) (Kudinov and Darbar, 2020). In a hypertensive rat model, Du and colleagues demonstrated that acute treatment with ibrutinib induced ventricular fibrillation in older rats. This was achieved through enhanced action potential duration alternans and spatial discordance, a lower calcium alternans ratio, and a shorter time to peak calcium amplitude. In contrast, ibrutinib did not induce these changes or trigger ventricular arrhythmias in younger rats (Du et al., 2020). The molecular pathways through which ibrutinib induces these alterations remain inadequately understood.

3.1.2 Acalabrutinib (ACP-196)

Acalabrutinib (ACP-196) (Table 1) is a second-generation, selective, irreversible inhibitor of BTK that has improved pharmacologic features, including favorable plasma exposure, rapid oral absorption, a short half-life, and the absence of irreversible targeting to alternative kinases, such as epidermal growth factor receptor (EGFR), TEC, and ITK (Byrd et al., 2016). In kinase-inhibition assays, acalabrutinib was a more selective BTK inhibitor than ibrutinib (Byrd et al., 2016). Unlike ibrutinib, acalabrutinib did not inhibit EGFR, ITK, or TEC (Byrd et al., 2016). In the *in vitro* assays, it was clearly demonstrated that, unlike ibrutinib, acalabrutinib had no effect on the phosphorylation of EGFR at tyrosine residues Y1068 and Y1173. At a concentration of 1,000 nM, ibrutinib completely suppressed TEC activity, whereas acalabrutinib at the same concentration exhibited minimal activity on TEC (Byrd et al., 2016). Compared to ibrutinib, acalabrutinib exhibits a significantly higher IC50 (>1,000 nM) and essentially no inhibition of kinase activities for ITK, EGFR, ERBB2, ERBB4, JAK3, BLK, FGR, FYN, HCK, LCK, LYN, SRC and YES1 (Byrd et al., 2016; Christensen et al., 2022).

In two separate pooled safety analyses of acalabrutinib monotherapy trials for a variety of B cell malignancies totaling 1802 patients, the incidence of AF was 4% (Brown et al., 2020; Furman et al., 2021). The majority of patients who developed AF in these trials had preceding cardiovascular risk factors prior to starting acalabrutinib. In both analyses, the median time to AF occurrence was 521 days and in contrast to ibrutinib, the incidence did not increase over time (Brown et al., 2020; Furman et al., 2021). No patients in the acalabrutinib arm discontinued therapy due to AF compared to 3.4% of patients in the ibrutinib arm (Byrd et al., 2021).

Hypertension has been reported in 5%–9% of patients in clinical trials of acalabrutinib monotherapy (Brown et al., 2020; Byrd et al., 2021; Furman et al., 2021; Owen et al., 2020). No patients in the acalabrutinib group discontinued therapy due to hypertension. Although the rates of hypertension are relatively lower with acalabrutinib compared to ibrutinib, the increased incidence of hypertension in acalabrutinib trials suggests that hypertension could be an effect associated with the BTKi class (Table 2).

The mechanism of acalabrutinib-induced AF is not well understood. Unlike ibrutinib, acalabrutinib does not inhibit CSK in mouse models (Xiao et al., 2020). Furthermore, acalabrutinib does not effectively inhibit other kinases associated with hypertension, such as EGFR or TEC (Estupiñán et al., 2021). Acalabrutinib-induced AF is primarily attributed to its impact on cardiomyocyte intracellular calcium management, specifically through the modulation of CaMK II and RyR pathways.

Like the hypertension caused by ibrutinib, the mechanism of hypertension linked to acalabrutinib remains not well understood. As it exerts a similar effect on TEC kinase as ibrutinib, it is plausible that the downstream PI3K downregulation as a result of TEC inhibition may alter the vascular endothelium via decreased nitric oxide production (Ghia et al., 2020; McMullen et al., 2014). Further studies are needed to elucidate the underlying mechanism, which may uncover novel pathways involved in the development of hypertension.

3.1.3 Zanubrutinib (BGB-3111)

Zanubrutinib (BGB-3111) is a second-generation irreversible BTKi (Table 1). Compared to ibrutinib, zanubrutinib exhibits heightened selectivity for BTK over ITK, leading to reduced inhibition of antigen-dependent cell-mediated cytotoxicity *in vitro*. However, it shows lower overall kinase selectivity for BTK when compared to acalabrutinib or tirabrutinib (Bond and Woyach, 2019). Zanubrutinib also inhibits off-target kinases, including EGFR, ITK, BMX, and the relaxin-Tec tyrosine kinase protein (RLX-TXK) (Estupiñán et al., 2021; Lipsky and Lamanna, 2020).

In the Phase III ASPEN trial, which compared zanubrutinib to ibrutinib in 201 patients with Waldenström's macroglobulinemia, AF was reported in only 2% of patients treated with zanubrutinib. There were no grade 3 AF events in the zanubrutinib arm and it was not discontinued for AF in any patient. The ASPEN study revealed hypertension incidence at 11% (including 6% at grade ≥ 3) among patients receiving zanubrutinib (Tam et al., 2020). The incidence and severity of most BTK-related toxicities, including AF, were lower with zanubrutinib than with ibrutinib (Tam et al., 2020). The treatment with zanubrutinib was associated with a trend towards improved response quality and reduced toxicity, particularly cardiovascular toxicity (Tam et al., 2020). No cases of VAs or sudden cardiac deaths have been reported in published clinical trials or post-marketing studies of zanubrutinib to date (Table 2) (An et al., 2021; Song et al., 2020; Tam et al., 2020).

3.1.4 Tirabrutinib (Velebru®)

Tirabrutinib (Velebru®) is another covalent inhibitor currently approved only in Japan (Table 1). It is an oral medication that specifically targets and inhibits BTK by forming a covalent bond with C481, effectively blocking BCR signaling and thereby reducing

TABLE 3 Research status of BTK inhibitors in the clinical trials.

| Drug | Characteristic(s) | Disease(s) | R&D progress and R&D company | IC50 (nM) | | | | | References(s) |
|---|--|--|---|-----------|---------|--------|------|--------|--|
| | | | | BTK | ITK | TEC | BMX | TXK | |
| Branerutinib (BMS-986195) | Covalent (Irreversible) BTKi | SLE, RA | Phase Ib Bristol-Myers Squibb | 0.1 | 100 | 0.9 | 1.5 | 5 | Watterson et al. (2019) |
| Nemtabrutinib (ARQ-531) (MK-1026) | Non-covalent (Reversible) BTKi Highly selective, covalent C481S mutant BTK | R/R CLL, NHL, WM (Phase I/II), CLL, SLL (Phase III) | Phase III Merck | 0.85 | >10,000 | 5.8 | 5.2 | 36 | Woyach et al. (2022), Woyach et al. (2024) |
| Spebrutinib (CC-292/AVL292) | Covalent (Irreversible) BTKi Highly selective, covalent oral small-molecule | CLL/SLL, B cell NHL, WM(Phase I) | Phase II Celgene/Avila Therapeutics | 2.3 | 24 | 16 | 1.6 | 9.1 | Brown et al. (2016), Evans et al. (2013) |
| Evobrutinib (M2951, MSC-236447C) | Covalent (Irreversible) BTKi | MS (Phase II), SLE, MS (Phase III) | Phase III Merck | 8.9 | NA | 7,300 | 20 | NA | Haselmayer et al. (2019) |
| Vecabrutinib (SNS-062) | non-covalent (Reversible) BTKi | R/R CLL, other B cell malignancies (Phase Ib/II) | Phase Ib/II Not to proceed with phase II studies | 3 | 14 | 14 | 224 | 474 | Jebaraj et al. (2022) |
| Fenebrutinib (GDC-0853) | non-covalent (Reversible) BTKi Less off-target activity | R/R B-NHL and CLL (Phase I), RA, SLE, CSU, MS (Phase II) | Phase III Genentech | 2.3 | >1,000 | >1,000 | 351 | >1,000 | Crawford et al. (2018) |
| Remibrutinib (LOU064) | Covalent (Irreversible) BTKi | CSU, MS | Phase II Novartis | 1.3 | NA | NA | NA | NA | Lin et al. (2024) |
| Poseltinib (HM-71224) | Covalent (Irreversible) BTKi | Refractory CNSL, DLBCL, PCNSL, RA | Phase II Hanmi Pharmaceutical/Eli Lilly | 1.95 | 103 | 4.57 | 0.64 | 4.62 | Park et al. (2016), Byun et al. (2021) |
| Elsubrutinib (ABBV-105) | An orally active, potent, selective and irreversible BTKi | Inflammatory disease | Phase II AbbVie, Inc. | 0.18 | NA | NA | NA | NA | Goess et al. (2019) |
| Edralbrutinib (EBI-1459) (SHR-1459) (TG-1701) | An orally available, irreversible BTKi | B-NHL, CLL | Phase II Eternity Bioscience, Inc. | 6.7 | NA | NA | NA | NA | Ribeiro et al. (2021) |
| Rilzabrutinib (PRN1008) | Covalent (Irreversible) BTKi | ITP, immune-mediated diseases | Phase III Sanofi/Principia Biopharma | 1.3 | 440 | 0.8 | 1.0 | 1.2 | Langrish et al. (2021) |
| Tolebrutinib (SAR442168, PRN2246) | Covalent (Irreversible) BTKi | MS | Phase III Sanofi/Principia Biopharma | 0.7 | NA | NA | NA | NA | Owens et al. (2022) |
| BMS-935177 | A potent and selective reversible BTKi | Autoimmune diseases | Phase I Bristol Myers Squibb Co. | 3.0 | 96 | 13 | 24 | 180 | De Lucca et al. (2016) |

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; R/R CLL, relapsed/refractory chronic lymphocytic leukemia; NHL, non-hodgkin lymphoma; WM, Waldenström's macroglobulinemia; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; MS, multiple sclerosis; RA, rheumatoid arthritis; CSU, chronic spontaneous urticaria; CNSL, central nervous system lymphoma; DLBCL, diffuse large B cell lymphoma; PCNSL, primary central nervous system lymphoma; B-NHL, B cell non-Hodgkin lymphoma; ITP, immunologic thrombocytopenic purpura; NA, no data.

the proliferation of malignant B cells. The Pharmaceuticals and Medical Devices Agency (PMDA) granted approval in 2020 for the treatment of relapsed/refractory primary central nervous system lymphoma (R/R PCNSL) (Dhillon, 2020; Gupta et al., 2025). Tirabrutinib exhibits a kinome profile analogous to acalabrutinib, characterized by high specificity for BTK, moderate inhibition of TEC, and negligible activity against EGFR, ERBB2-HER2, ITK, and JAK3 (Estupiñán et al., 2021). By the end of 2023, a total of 18 patients were enrolled in 9 hospitals in Taiwan, among whom

atrial fibrillation was found (Liao et al., 2024). In addition, no major cardiovascular adverse events were reported.

3.1.5 Orelabrutinib

Orelabrutinib is another highly potent, orally administered, covalent BTK inhibitor that exhibits strong selectivity for BTK, minimizing off-target effects (Table 1). In 2020, it received approval from China's National Medical Products Administration (NMPA) for the treatment of patients with relapsed/refractory chronic

TABLE 4 Research status of BTK inhibitors in the preclinical trials.

| Drug | Characteristic(s) | Disease(s) | R&D progress and R&D company | IC50 (nM) | | | | | References(s) |
|----------|---------------------------------|------------|--------------------------------------|-----------|-------|---------|------|-----|------------------------|
| | | | | BTK | ITK | TEC | BMX | TXK | |
| RN-486 | Non-covalent (Reversible) BTKi | RA, SLE | Pre-clinical F. Hoffmann-La Roche | 4.0 | NA | NA | NA | NA | Xu et al. (2012) |
| GDC-0834 | Non-covalent (Reversible) BTKi | RA | Pre-clinical Genentech/Gilead | 5.9 | NA | NA | NA | NA | Liu et al. (2011) |
| CGI-1746 | Non-covalent (Reversible) BTKis | RA | Pre-clinical CGI Pharmaceuticals | 1.9 | 4,270 | >10,000 | 1870 | NA | Di Paolo et al. (2011) |
| CNX-774 | Covalent (Irreversible) BTKi | NA | Pre-clinical Avila Therapeutics | <1.0 | NA | NA | NA | NA | Akinleye et al. (2013) |
| JS25 | A selective and covalent BTKi | CLL | Pre-clinical | 5.8 | 440 | 220 | 49 | 190 | Sousa et al. (2022) |

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; CLL, chronic lymphocytic leukemia; NA, no data.

lymphocytic leukemia (R/R CLL) or small lymphocytic lymphoma (SLL), as well as relapsed/refractory mantle cell lymphoma (R/R MCL) who had previously undergone at least one prior treatment (Deng et al., 2023; Gupta et al., 2025). In 2023, orelabrutinib expanded its therapeutic application and was approved in China for the treatment of relapsed/refractory marginal zone lymphoma (R/R MZL). Furthermore, the U.S. Food and Drug Administration (FDA) granted the drug a breakthrough therapy designation (BTD) for the treatment of R/R MCL. In published pivotal clinical trials and real-world studies, the incidence of atrial fibrillation is extremely low (usually reported as 0% or <1%) (Cao et al., 2023; Xu W. et al., 2019).

3.1.6 Pirtobrutinib

Pirtobrutinib (Jaypirca[®]) is a highly selective, orally administered, non-covalent BTK inhibitor that received accelerated FDA approval in January 2023 for the treatment of R/R MCL after at least two prior lines of therapy, including a previous BTKi (Table 1) (Gupta et al., 2025; Keam, 2023; Wang et al., 2023). Grade ≥ 3 treatment-emergent adverse events (TEAEs) of hemorrhage (3.7%) and atrial fibrillation/flutter (1.2%) were relatively infrequent (Wang et al., 2023). Of the 323 patients in the trial, only 2 developed AF, both of whom had a history of AF prior to the study's initiation. 5% (1% grade 3) of patients developed hypertension during the study, with a median follow-up of 6 months. Notably, among the 15 patients who discontinued a previous BTKi due to cardiotoxicity, none experienced a recurrent cardiac adverse event while taking pirtobrutinib (Table 2) (Mato et al., 2021). The incidence of cardiovascular toxicity (particularly atrial fibrillation and hypertension) of Pirtobrutinib is significantly lower than that of traditional BTK inhibitors such as Ibrutinib (Shah et al., 2024).

3.1.7 Fenebrutinib

Fenebrutinib is an orally administered BTKi designed for the treatment of autoimmune diseases and lymphoma, with reduced off-target activity (Table 3). Unlike covalent BTK inhibitors such as ibrutinib and acalabrutinib, fenebrutinib binds to BTK non-covalently, enabling it to target both wild-type BTK and BTK with C481S mutations, a common resistance mechanism to first-generation covalent inhibitors (Crawford et al., 2018; Gupta et al., 2025). No cases of AF or hypertension were reported among the

307 study patients who received fenebrutinib, although only adverse events occurring at a frequency of 5% or greater were documented (Cohen et al., 2020), indicating that it has no obvious cardiovascular toxicity signal.

3.1.8 Other BTKi

Other BTK inhibitors are summarized in Tables 3, 4. Branebrutinib (BMS-986195) is a potent, highly selective, oral small-molecule covalent BTKi (Catlett et al., 2020; Watterson et al., 2019). Evobrutinib is also a covalent BTKi that effectively inhibits BTK activity in both B cells and myeloid cells, both of which are pivotal in mediating immune responses. By targeting these pathways, evobrutinib aims to reduce inflammation and autoimmunity (Caldwell et al., 2019; Haselmayer et al., 2019). Spebrutinib is a highly selective, covalent oral small-molecule BTKi that targets the same C481 residue in BTK as ibrutinib, thereby blocking BTK signaling. Preclinical studies demonstrated that spebrutinib effectively inhibited B cell activation dependent on BCR (Brown et al., 2016). Nemtabrutinib, previously known as ARQ-531, is a noncovalent BTKi designed to target both wild-type (WT) and C481S mutant BTK, including resistance mutations. It is being explored as a treatment for R/R CLL/SLL and other hematological malignancies (Woyach et al., 2022). Vecabrutinib is another orally administered noncovalent BTKi designed to target both WT BTK and BTK with the C481S mutation, a common mutation that confers resistance to ibrutinib and acalabrutinib. Vecabrutinib functions by inhibiting the phosphorylation of BTK, thereby blocking the activity of its downstream target, phosphatidylinositol-specific phospholipase C γ 2 (PLC γ 2). Despite generally being well tolerated, the lack of efficacy and observed adverse effects led to the decision not to proceed with Phase II studies (Cohen et al., 2020).

3.2 BMX inhibitors

In contrast to BTK, the development of inhibitors for other TEC kinases has been relatively limited, despite considerable evidence indicating their significant roles in hematopoiesis and their potential as therapeutic targets (Forster et al., 2020). Table 5 summarizes the related contents of BMX inhibitors in previous studies.

TABLE 5 Research status of BMX, ITK, TXK and TEC inhibitors.

| Drug | Characteristic(s) | Disease(s) | R&D progress and R&D company | IC50 (nM) | | | | | References(s) |
|------------------------------------|---|---|--|-----------|--------|--------|---------|--------|---|
| | | | | BTK | ITK | TEC | BMX | TXK | |
| BMX-IN-1 | A potent, selective, and irreversible BMX kinase inhibitor | Prostate cancer | Pre-clinical | 10.4 | 5,250 | 653 | 8 | 377 | Liu F. et al. (2013) |
| CHMFL-BMX-078 | A highly selective type II irreversible BMX inhibitor | Melanoma | Pre-clinical | 437 | NA | NA | 11 | NA | Liang et al. (2017), Jiang et al. (2022) |
| IHMT-15130 | A highly potent and selective irreversible BMX inhibitor | Cardiac hypertrophy | Pre-clinical | NA | NA | NA | 1.47 | NA | Qi et al. (2025) |
| Soquelitinib (CPI-818) | An orally active and highly selective covalent ITK inhibitor | T Cell Lymphoma | Phase 1b/2 Akros Pharma, Inc. | NA | NA | NA | NA | NA | Hsu et al. (2024) |
| JTE-051 | A selective ITK inhibitor | Immune system diseases | Phase II Angel Pharmaceuticals Co., Ltd. | NA | NA | NA | NA | NA | Zarrin et al., (2021), Study to Evaluate Efficacy (2025) |
| PRN694 | Irreversible, highly selective and potent covalent ITK and RLK dual inhibitor | Psoriasis, autoimmune, inflammatory, malignant diseases | Pre-clinical | 17 | 0.3 | 3.3 | 17 | 1.4 | Zhong et al. (2015), Cho et al. (2015) |
| BMS-509744 | Potently and selectively inhibits ITK kinase activity | Psoriasis | Pre-clinical | 4,100 | 19 | 17,000 | >50,000 | 11,000 | Lin et al. (2004) |
| BSJ-05-037 | A potent and selective heterobifunctional degrader of ITK | Psoriasis | Pre-clinical | NA | 17.6 | NA | NA | NA | Jiang et al. (2023) |
| Acalabrutinib/ Calquence (ACP-196) | The selectivity of TXK is 19 times lower than that of BTK, but there is still cross-inhibition. | Untreated or refractory CLL/ SLL, pretreated MCL | Approved by FDA and EMA in 2017 AstraZeneca/Acerta Pharma BV | 5.1 | >1,000 | 93 | 46 | 368 | Byrd et al. (2016), Acalabrutinib, (2012), Markham and Dhillon (2018) |
| Ritlecitinib (PF-06651,600) | Irreversible inhibitor of JAK3 and TEC kinase family | AA, Vitiligo, UC | Approved by FDA and EMA in 2023 Pfizer Inc. | 607 | 8,510 | 592 | 606 | 193 | Thorarensen et al. (2017), Telliez et al. (2016) |

CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; MCL, mantle cell lymphoma; AA, alopecia areata; UC, ulcerative colitis; NA, no data.

BMX-IN-1 is a potent, selective, and irreversible inhibitor of BMX kinase, which covalently modifies Cys496 (Liu F. et al., 2013). CHMFL-BMX-078 is a highly selective and potent type II irreversible inhibitor of BMX kinase. It demonstrated an IC50 of 11 nM by forming a covalent bond with the Cys496 residue in the DFG-out inactive conformation of BMX (Liang et al., 2017). IHMT-15130 is a potent and irreversible BMX kinase inhibitor that covalently targets cysteine 496 of BMX and exhibits potent inhibitory activity against BMX kinase. IHMT-15130 shows selectivity for CSK kinase, and its targeting of CSK may lead to severe atrial fibrillation and bleeding (Qi et al., 2025). All agents are in preclinical studies, and none has been reported to exhibit cardiovascular toxicity.

In the context of cardiovascular pathology, BMX has been reported to be upregulated in atherosclerotic plaques, models of myocardial ischemia-reperfusion injury, and heart failure models, potentially contributing to disease progression by exacerbating inflammation and driving pathological remodeling (Holopainen et al., 2015; Qi et al., 2025). Theoretically, therefore, BMX inhibition may impact the cardiovascular system by disrupting endothelial homeostasis, vascular repair processes, and myocardial adaptive responses. Currently, highly selective BMX

inhibitors (e.g., BMX-IN-1, CHMFL-BMX-078) remain in the preclinical stage, with no systematic reports of cardiovascular toxicity to date (Jiang et al., 2022; Liang et al., 2017; Liu F. et al., 2013). Notably, the first-generation BTK inhibitor ibrutinib also acts as a potent BMX inhibitor (Table 1) (Burger and Buggy, 2013; Qiu et al., 2014). Whether the cardiovascular toxicities observed clinically with ibrutinib, particularly hypertension, which may involve endothelial dysfunction, are partially attributable to BMX inhibition represents an open question warranting further investigation (Shirley, 2022). This highlights that endothelial function, blood pressure, and cardiac remodeling should be considered key safety endpoints during the development of BMX-targeted or broad-spectrum TEC family kinase inhibitors.

3.3 ITK inhibitors

Soquelitinib (CPI-818) is an orally active and highly selective covalent ITK inhibitor and is a potential novel target to enhance the immunotherapy of cancer (Hsu et al., 2024). Currently, Phase 1b/2 clinical trials of this agent are underway in China. JTE-051 is another ITK inhibitor currently under clinical evaluation for the

TABLE 6 Summary of cardiotoxicity of TEC family kinase inhibitors.

| Drug | Toxicity Phenotype | Proposed Mechanism(s) | Key Evidence |
|--|--|---|---|
| Ibrutinib (1st-gen covalent BTKi) | AF (5%–16% incidence) | Off-target inhibition of C-terminal Src kinase (CSK) → increased Src family kinase (SFK) activity → atrial fibrosis and inflammation via NLRP3 inflammasome. Altered cardiomyocyte Ca ²⁺ handling via CaMKII/RyR2 pathway. | Clinical trials and real-world analyses show AF leading to drug discontinuation in 20%–60% of cases where it occurs (Maddocks et al., 2015; Wiczer et al., 2017). Mouse model with cardiomyocyte-specific CSK knockout recapitulates AF phenotype (Xiao et al., 2020). |
| | Hypertension (up to 80% in real-world studies) | Reduced secretion of VEGF and homeostatic chemokines → decreased nitric oxide (NO) production → increased vascular tone. Downregulation of PI3K pathway via BTK/TEC inhibition may contribute to vascular remodeling. | Reported in up to 30% of patients in trials, up to 80% in real-world studies (Dickerson et al., 2019). Retrospective analysis shows increased risk vs. chemotherapy (Abdel-Qadir et al., 2021). |
| Ibrutinib (1st-gen covalent BTKi) | VAs and HF | Acute dysregulation of cardiomyocyte Ca ²⁺ handling and repolarization. Long-term mechanisms may involve pro-fibrotic and inflammatory pathways. | Case reports and retrospective analyses link ibrutinib to VAs (Guha et al., 2018; Kudinov and Darbar, 2020). Long-term follow-up data indicate up to 5% HF incidence (Barr et al., 2022; Munir et al., 2019); 3-year risk of 7.7% in one analysis (Abdel-Qadir et al., 2021). Hypertensive rat model shows acute induction of ventricular fibrillation (Du et al., 2020). |
| Acalabrutinib (2nd-gen covalent BTKi) | AF (~4% incidence) | Primarily attributed to impact on cardiomyocyte intracellular Ca ²⁺ management (CaMKII/RyR pathways). Does not significantly inhibit CSK. | Pooled safety analyses of trials (n = 1802) report 4% AF incidence, median time to event 521 days, no increase over time (Brown et al., 2020; Furman et al., 2021). Lower discontinuation rate due to AF vs. ibrutinib (Byrd et al., 2021). |
| | Hypertension (5%–9% incidence) | Mechanism not fully understood. Similar to ibrutinib, potential role of TEC inhibition and downstream PI3K downregulation affecting vascular endothelium and NO production. | Reported in clinical trials (Brown et al., 2020; Byrd et al., 2021; Furman et al., 2021; Owen et al., 2020). Incidence suggests it may be a class effect, but less frequent/severe than with ibrutinib. |
| Zanubrutinib (2nd-gen covalent BTKi) | AF (~2% incidence) | Not explicitly detailed, but improved selectivity profile (over ITK, etc.) likely reduces off-target toxicity. | In ASPEN trial vs. ibrutinib, only 2% AF reported (0% grade 3, no discontinuations) (Tam et al., 2020). |
| | Hypertension (11% incidence, 6% ≥grade 3) | Mechanism not specified, but off-target kinase profile differs from ibrutinib. | Reported in ASPEN trial (Tam et al., 2020). |
| Pirtobrutinib (Non-covalent BTKi) | Atrial Fibrillation/Flutter (1.2% grade ≥3) | Mechanism not studied. Hypothesized that reversible, non-covalent binding and high selectivity may minimize off-target effects. | In BRUIN trial (n = 323), only 2 patients developed AF (both had prior history) (Mato et al., 2021; Wang et al., 2023). No recurrent cardiac events in patients who discontinued prior BTKi due to cardiotoxicity (Mato et al., 2021). |
| | Hypertension (5% incidence, 1% grade 3) | Mechanism not specified. | Reported in BRUIN trial with 6-month median follow-up (Mato et al., 2021; Wang et al., 2023). |
| Fenebrutinib (Non-covalent BTKi) | No significant signal for AF or hypertension reported | High selectivity for BTK, minimal off-target activity. | In a phase II RA trial (n = 307), no cases of AF or hypertension were reported among documented AEs (≥5% frequency) (Cohen et al., 2020). |
| Ritlecitinib (JAK3/TEC inhibitor) | MACE (low incidence) | Mechanism not fully elucidated. Potential concern due to TEC inhibition affecting vascular endothelium (PI3K-AKT pathway) and platelet function. | In clinical trials for alopecia areata, low rates of adjudicated MACE reported (0.2% in 50-mg group). All patients with events had pre-existing CV risk factors (King et al., 2024; FDA, 2025). One unrelated death due to MI reported (Sandborn et al., 2023). |
| BMX Inhibitors (e.g., BMX-IN-1, CHMFL-BMX-078) | No systematic cardiovascular toxicity reported (preclinical stage) | Theoretically, BMX inhibition could disrupt endothelial homeostasis and vascular repair, given its role in atherosclerosis and myocardial remodeling models. | All are preclinical; no clinical CV toxicity data (Liang et al., 2017; Liu F et al., 2013). Ibrutinib's potent BMX inhibition raises the question of its contribution to ibrutinib's hypertension/endothelial toxicity (Shirley, 2022). |

(Continued on following page)

TABLE 6 (Continued) Summary of cardiotoxicity of TEC family kinase inhibitors.

| Drug | Toxicity Phenotype | Proposed Mechanism(s) | Key Evidence |
|--|--|--|---|
| ITK Inhibitors (e.g., Soquelitinib, JTE-051, PRN694) | No significant cardiovascular safety signals reported in current trials. | Primary action is immunomodulation via T-cells. May indirectly influence CVD progression (e.g., atherosclerosis) via systemic suppression of T cell-driven inflammation. | Clinical trials for autoimmune diseases; no major CV events highlighted in available data (Hsu et al., 2024; Zarrin et al., 2021; Zhong et al., 2015). Theoretical risk due to inflammation-CVD link warrants monitoring. |
| TXK Inhibitors | Low presumed risk of direct cardiovascular toxicity | Limited tissue expression (primarily lymphoid). No strong evidence linking TXK to cardiovascular function. | No highly selective TXK inhibitors in clinical development. Some multi-target inhibitors (e.g., PRN694) have TXK activity (Zhong et al., 2015). |

AF, atrial fibrillation; BTKi, Bruton's Tyrosine Kinase Inhibitor; CaMKII, Calcium/calmodulin-dependent protein kinase II; CSK, C-terminal Src kinase; CV, cardiovascular; CVD, cardiovascular disease; MACE, major adverse cardiovascular events; MI, myocardial infarction; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NO, nitric oxide; PI3K, Phosphatidylinositol 3-kinase; RyR2, Ryanodine Receptor 2; SFK, Src family kinase; TEC, tyrosine kinase expressed in hepatocellular carcinoma; VEGF, vascular endothelial growth factor.

treatment of rheumatoid arthritis (RA) and psoriasis (Table 5) (Zarrin et al., 2021). PRN694 is a highly selective and potent covalent inhibitor of ITK and TXK (Table 5); its extended target residence time allows for durable attenuation of effector cells (Zhong et al., 2015). This ITK/RLK dual inhibitor was approved for the treatments of T-cell or NK cell malignancies as well as inflammatory and autoimmune diseases, such as psoriasis, psoriatic arthritis, rheumatoid arthritis, multiple sclerosis, and irritable bowel disease (Fuhrman et al., 2018; Zhong et al., 2015). BMS-509744 is a potent and selective ITK inhibitor which inhibits anti-TCR antibody induced IL-2 production (Table 5) (Das et al., 2006; Lo, 2010).

While the role of ITK in adaptive immunity is well-established (Lechner et al., 2020), direct evidence for its expression and function in cardiovascular cells remains limited. However, T cell-driven inflammation is a critical mechanism in atherosclerosis, myocarditis, and certain cardiomyopathies (Chen et al., 2023; Rosenzweig et al., 2021). Thus, inhibition of ITK may indirectly influence the progression of cardiovascular diseases, such as atherosclerosis, through systemic immunosuppression and modulation of the inflammatory cytokine network. Currently, ITK inhibitors in clinical development are primarily targeting T cell-mediated autoimmune diseases. According to publicly available data from these trials, no significant cardiovascular safety signals have been reported. Nonetheless, given the close link between inflammation and cardiovascular diseases, it remains a prudent measure to monitor cardiovascular events in patients receiving long-term ITK inhibitor therapy.

3.4 TXK inhibitors

Similar to ITK, TXK is directly involved in TCR signaling. To date, no highly selective TXK inhibitors have entered clinical development. Some multi-target inhibitors (e.g., PRN694) also exhibit activity against TXK (Zhong et al., 2015). Given its more restricted tissue expression, primarily limited to lymphoid lineages, and the scarcity of studies linking TXK to cardiovascular functions (Kashiwakura et al., 1999), it is generally considered that inhibiting TXK carries a low risk of direct cardiovascular toxicity (Yin et al., 2022). However, this conclusion still requires further verification through future studies employing specific pharmacological tools and more in-depth investigation.

3.5 TEC inhibitors

Ritlecitinib (LITFULO™) is a kinase inhibitor being developed by Pfizer for the treatment of alopecia areata, vitiligo, ulcerative colitis, and Crohn's disease. Ritlecitinib irreversibly inhibits JAK3 and the TEC kinase (Table 5) (Blair, 2023; Xu H. et al., 2019). Among the 319 randomized patients, there was one death due to myocardial infarction, which was considered unrelated to the study drug (Sandborn et al., 2023). No major adverse cardiovascular events, opportunistic infections, or deaths were reported (Hordinsky et al., 2023; King et al., 2023; King et al., 2021). However, it is necessary to pay attention to its effects on the vascular endothelium (BMX inhibition) and the PI3K-AKT pathway, as these may increase the risk of bleeding or myocardial injury. In another study, within the all-exposure pool for the ritlecitinib 50-mg group, three patients (0.2%) with adjudicated Major Adverse Cardiovascular Events (MACE) as serious adverse events were reported (King et al., 2024; FDA, 2025). Notably, patients with cardiovascular risk factors were not specifically excluded from the ALLEGRO studies, and all patients who experienced cardiovascular events had at least one cardiovascular risk factor (King et al., 2024). Thrombosis has occurred in patients treated with LITFULO (FDA, 2025). The relationship between thromboembolic and cardiovascular events and the increased lipid levels observed with some JAK inhibitors is not well understood (Gladman et al., 2019).

In the cardiovascular context, TEC plays a role in VEGF and shear stress-induced endothelial cell signaling, potentially affecting angiogenesis and endothelial barrier function (Kluppel et al., 1997). Furthermore, TEC is also involved in platelet activation signaling (Atkinson et al., 2003). Therefore, inhibition of TEC may potentially influence vascular integrity, thrombus formation, and vascular remodeling processes. Although preliminary clinical cardiovascular safety data for ritlecitinib indicate a relatively low risk, theoretical concerns remain regarding its impact on vascular endothelium and the PI3K-AKT pathway, which may be associated with bleeding tendency or alterations in vascular function (Herrmann, 2020). Inhibition of TEC by BTK inhibitors such as ibrutinib (Table 1) may also contribute to their toxicity profile. In the future, developing more selective TEC inhibitors combined with refined cardiovascular function assessments will help elucidate the independent contribution of TEC inhibition to cardiovascular toxicity.

4 Conclusion

TFKs represent a class of transformative therapeutics, yet their associated cardiovascular toxicity remains a significant clinical challenge (Table 6). This review synthesizes current evidence, yielding several key insights. First, cardiovascular toxicity is a well-established class effect of BTKs, with its incidence and severity inversely correlating with kinase selectivity; AF and hypertension are the most frequently observed events (Quartermaine et al., 2023). Second, the underlying mechanisms arise from a combination of on-target BTK inhibition and off-target inhibition of other kinases such as CSK and TEC. Key implicated pathways include dysregulated calcium handling (CaMKII/RyR2), inflammation (NLRP3), fibrosis, and endothelial dysfunction (VEGF/PI3K-NO) (Kudinov and Darbar, 2020; N. Liu et al., 2013; McMullen et al., 2014; Pandey et al., 2018; Ping et al., 2017). While the cardiovascular toxicity of BTK inhibitors has garnered substantial attention, future research urgently needs to extend to inhibitors targeting other TEC family kinases and long-term cardiovascular safety data for inhibitors specifically targeting other TFK members remain scarce. Regarding BMX, highly selective inhibitors should be developed and systematically evaluated in models such as atherosclerosis and myocardial hypertrophy to assess their effects on vascular endothelium and myocardial remodeling. For ITK, it is necessary to clarify its role in T cell-mediated cardiovascular inflammation (e.g., atherosclerosis) and to explore the balance between its immunomodulatory effects and cardiovascular safety. Although TXK has limited direct cardiovascular actions, its immunomodulatory potential still requires validation through specific tool compounds. Concerning TEC, long-term clinical follow-up should focus on endothelial function, platelet activation, and the PI3K-AKT pathway, particularly in populations at high cardiovascular risk.

Given their distinct tissue distributions and functions, these agents may present different risk profiles, a possibility that urgently warrants targeted investigation. From a clinical management standpoint, important strategies include opting for newer, more selective agents, conducting proactive cardiovascular risk assessments, implementing enhanced monitoring, and fostering multidisciplinary care within a cardio-oncology framework.

Author contributions

YZ: Writing – original draft, Visualization, Investigation, Data curation, Writing – review and editing. HF: Writing – original draft, Visualization. XK: Visualization, Writing – original draft. ZQ: Data

curation, Writing – original draft, Visualization. HY: Writing – review and editing. QH: Writing – review and editing, Conceptualization, Project administration. BY: Writing – review and editing, Project administration, Conceptualization. ZX: Conceptualization, Funding acquisition, Visualization, Writing – review and editing, Project administration, Supervision. PL: Visualization, Project administration, Writing – review and editing, Conceptualization.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

- Abdel-Qadir, H., Sabrie, N., Leong, D., Pang, A., Austin, P. C., Prica, A., et al. (2021). Cardiovascular risk associated with ibrutinib use in chronic lymphocytic leukemia: a population-based cohort study. *JCO* 39, 3453–3462. doi:10.1200/JCO.21.00693
- Acalabrutinib (2012). in *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* (Bethesda: National Institute of Diabetes and Digestive and Kidney Diseases).
- Akinleye, A., Chen, Y., Mukhi, N., Song, Y., and Liu, D. (2013). Ibrutinib and novel BTK inhibitors in clinical development. *J. Hematol. Oncol.* 6, 59. doi:10.1186/1756-8722-6-59
- An, Y., and Zhang, F. (2024). A review of TEC family kinases and their inhibitors in the treatment of alopecia areata. *Arch. Dermatol Res.* 316, 496. doi:10.1007/s00403-024-03229-0
- An, G., Zhou, D., Cheng, S., Zhou, K., Li, J., Zhou, J., et al. (2021). A phase II trial of the Bruton Tyrosine-kinase inhibitor Zanubrutinib (BGB-3111) in patients with relapsed/refractory waldenström macroglobulinemia. *Clin. Cancer Res.* 27, 5492–5501. doi:10.1158/1078-0432.CCR-21-0539
- Andersen, T. C. B., Kristiansen, P. E., Huszenicza, Z., Johansson, M. U., Gopalakrishnan, R. P., Kjelstrup, H., et al. (2019). The SH3 domains of the protein kinases ITK and LCK compete for adjacent sites on T cell-specific adapter protein. *J. Biol. Chem.* 294, 15480–15494. doi:10.1074/jbc.RA119.008318
- Atkinson, B. T., Ellmeier, W., and Watson, S. P. (2003). Tec regulates platelet activation by GPVI in the absence of Btk. *Blood* 102, 3592–3599. doi:10.1182/blood-2003-04-1142

- Awan, F. T., Tong, D., and Zaha, V. G. (2020). Cardio-oncology: a win-win situation. *Circulation* 142, 2456–2458. doi:10.1161/CIRCULATIONAHA.120.052047
- Barr, P. M., Owen, C., Robak, T., Tedeschi, A., Bairey, O., Burger, J. A., et al. (2022). Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv.* 6, 3440–3450. doi:10.1182/bloodadvances.2021006434
- Blair, H. A. (2023). Ritlecitinib: first approval. *Drugs* 83, 1315–1321. doi:10.1007/s40265-023-01928-y
- Bond, D. A., and Woyach, J. A. (2019). Targeting BTK in CLL: beyond ibrutinib. *Curr. Hematol. Malig. Rep.* 14, 197–205. doi:10.1007/s11899-019-00512-0
- Brown, J. R., Harb, W. A., Hill, B. T., Gabrilove, J., Sharman, J. P., Schreeder, M. T., et al. (2016). Phase I study of single-agent CC-292, a highly selective Bruton's tyrosine kinase inhibitor, in relapsed/refractory chronic lymphocytic leukemia. *Haematologica* 101, e295–e298. doi:10.3324/haematol.2015.140806
- Brown, J. R., Byrd, J. C., Ghia, P., Sharman, J. P., Hillmen, P., Stephens, D. M., et al. (2020). Pooled analysis of cardiovascular events from clinical trials evaluating acalabrutinib monotherapy in patients with chronic lymphocytic leukemia (CLL). *Blood* 136, 52–54. doi:10.1182/blood-2020-134797
- Burger, J. A., and Buggy, J. J. (2013). Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765). *Leuk. Lymphoma* 54, 2385–2391. doi:10.3109/10428194.2013.777837
- Byrd, J. C., Harrington, B., O'Brien, S., Jones, J. A., Schuh, A., Devereux, S., et al. (2016). Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N. Engl. J. Med.* 374, 323–332. doi:10.1056/NEJMoa1509981
- Byrd, J. C., Hillmen, P., Ghia, P., Kater, A. P., Chanan-Khan, A., Furman, R. R., et al. (2021). Acalabrutinib Versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. *J. Clin. Oncol.* 39, 3441–3452. doi:10.1200/JCO.21.01210
- Byun, J.-Y., Koh, Y. T., Jang, S. Y., Witcher, J. W., Chan, J. R., Pustilnik, A., et al. (2021). Target modulation and pharmacokinetics/pharmacodynamics translation of the BTK inhibitor poseltinib for model-informed phase II dose selection. *Sci. Rep.* 11, 18671. doi:10.1038/s41598-021-98255-7
- Caldwell, R. D., Qiu, H., Askew, B. C., Bender, A. T., Brugger, N., Camps, M., et al. (2019). Discovery of evobrutinib: an oral, potent, and highly selective, covalent bruton's tyrosine kinase (BTK) inhibitor for the treatment of immunological diseases. *J. Med. Chem.* 62, 7643–7655. doi:10.1021/acs.jmedchem.9b00794
- Cameron, F., and Sanford, M. (2014). Ibrutinib: first global approval. *Drugs* 74, 263–271. doi:10.1007/s40265-014-0178-8
- Cao, X., Jin, J., Cheng Cheng, F., Yi, S., Zhao, W., Sun, Z., et al. (2023). Orelabrutinib monotherapy in patients with relapsed or refractory Waldenström's macroglobulinemia in a single-arm, multicenter, open-label, phase 2 study: long term Follow-up results. *Blood* 142, 3039. doi:10.1182/blood-2023-181500
- Catlett, I. M., Nowak, M., Kundu, S., Zheng, N., Liu, A., He, B., et al. (2020). Safety, pharmacokinetics and pharmacodynamics of branebrutinib (BMS-986195), a covalent, irreversible inhibitor of Bruton's tyrosine kinase: randomised phase I, placebo-controlled trial in healthy participants. *Br. J. Clin. Pharmacol.* 86, 1849–1859. doi:10.1111/bcp.14290
- Chen, M., Xue, J., Wang, M., Yang, J., and Chen, T. (2023). Cardiovascular complications of pan-cancer therapies: the need for cardio-oncology. *Cancers (Basel)* 15, 3055. doi:10.3390/cancers15113055
- Cho, H.-S., Shin, H. M., Haberkstock-Debic, H., Xing, Y., Owens, T. D., Funk, J. O., et al. (2015). A small molecule inhibitor of ITK and RLK impairs Th1 differentiation and prevents colitis disease progression. *J. Immunol.* 195, 4822–4831. doi:10.4049/jimmunol.1501828
- Christensen, B. W., Zaha, V. G., and Awan, F. T. (2022). Cardiotoxicity of BTK inhibitors: ibrutinib and beyond. *Expert Rev. Hematol.* 15, 321–331. doi:10.1080/17474086.2022.2067526
- Cohen, S., Tuckwell, K., Katsumoto, T. R., Zhao, R., Galanter, J., Lee, C., et al. (2020). Fenebrutinib Versus placebo or adalimumab in rheumatoid arthritis: a randomized, double-blind, phase II trial. *Arthritis and Rheumatology* 72, 1435–1446. doi:10.1002/art.41275
- Crawford, J. J., Johnson, A. R., Misner, D. L., Belmont, L. D., Castaneda, G., Choy, R., et al. (2018). Discovery of GDC-0853: a potent, selective, and noncovalent bruton's tyrosine kinase inhibitor in early clinical development. *J. Med. Chem.* 61, 2227–2245. doi:10.1021/acs.jmedchem.7b01712
- Das, D., and Hong, J. (2020). Irreversible kinase inhibitors targeting cysteine residues and their applications in cancer therapy. *Mini Rev. Med. Chem.* 20, 1732–1753. doi:10.2174/1389557520666200513121524
- Das, J., Furch, J. A., Liu, C., Moquin, R. V., Lin, J., Spergel, S. H., et al. (2006). Discovery and SAR of 2-amino-5-(thioaryl)thiazoles as potent and selective Itk inhibitors. *Bioorg. and Med. Chem. Lett.* 16, 3706–3712. doi:10.1016/j.bmcl.2006.04.060
- De Lucca, G. V., Shi, Q., Liu, Q., Batt, D. G., Beaudoin Bertrand, M., Rampulla, R., et al. (2016). Small molecule reversible inhibitors of Bruton's tyrosine kinase (BTK): structure-activity relationships leading to the identification of 7-(2-Hydroxypropan-2-yl)-4-[2-methyl-3-(4-oxo-3,4-dihydroquinazolin-3-yl)phenyl]-9H-carbazole-1-carboxamide (BMS-935177). *J. Med. Chem.* 59, 7915–7935. doi:10.1021/acs.jmedchem.6b00722
- Deng, L.-J., Zhou, K.-S., Liu, L.-H., Zhang, M.-Z., Li, Z.-M., Ji, C.-Y., et al. (2023). Orelabrutinib for the treatment of relapsed or refractory MCL: a phase 1/2, open-label, multicenter, single-arm study. *Blood Adv.* 7, 4349–4357. doi:10.1182/bloodadvances.2022009168
- Dhillon, S. (2020). Tirabrutinib: first approval. *Drugs* 80, 835–840. doi:10.1007/s40265-020-01318-8
- Dhillon, S. (2021). Orelabrutinib: first approval. *Drugs* 81, 503–507. doi:10.1007/s40265-021-01482-5
- Di Paolo, J. A., Huang, T., Balazs, M., Barbosa, J., Barck, K. H., Bravo, B. J., et al. (2011). Specific btk inhibition suppresses B cell- and myeloid cell-mediated arthritis. *Nat. Chem. Biol.* 7, 41–50. doi:10.1038/nchembio.481
- Dickerson, T., Wiczter, T., Waller, A., Philippon, J., Porter, K., Haddad, D., et al. (2019). Hypertension and incident cardiovascular events following ibrutinib initiation. *Blood* 134, 1919–1928. doi:10.1182/blood.2019000840
- Du, B., Chakraborty, P., Azam, M. A., Massé, S., Lai, P. F. H., Niri, A., et al. (2020). Acute effects of ibrutinib on ventricular arrhythmia in spontaneously hypertensive rats. *JACC CardioOncology* 2, 614–629. doi:10.1016/j.jacc.2020.08.012
- Estupiñán, H. Y., Berglöf, A., Zain, R., and Smith, C. I. E. (2021). Comparative analysis of BTK inhibitors and mechanisms underlying adverse effects. *Front. Cell Dev. Biol.* 9, 630942. doi:10.3389/fcell.2021.630942
- Evans, E. K., Tester, R., Aslanian, S., Karp, R., Sheets, M., Labenski, M. T., et al. (2013). Inhibition of Btk with CC-292 provides early pharmacodynamic assessment of activity in mice and humans. *J. Pharmacol. Exp. Ther.* 346, 219–228. doi:10.1124/jpet.113.203489
- FDA (2025). *Novel drug approvals for 2023*. New York, NY: Pfizer Inc.
- Forster, M., Liang, X. J., Schröder, M., Gerstenecker, S., Chaikuad, A., Knapp, S., et al. (2020). Discovery of a novel class of covalent dual inhibitors targeting the protein kinases BMX and BTK. *Int. J. Mol. Sci.* 21, 9269. doi:10.3390/ijms21239269
- Fuhrman, J. M., Winge, M. C. G., Haberkstock-Debic, H., Funk, J. O., Bradshaw, J. M., and Marinkovich, M. P. (2018). ITK and RLK inhibitor PRN694 improves skin disease in two mouse models of psoriasis. *J. Invest. Dermatol.* 138, 864–871. doi:10.1016/j.jid.2017.10.029
- Furman, R. R., Byrd, J. C., Owen, R. G., O'Brien, S. M., Brown, J. R., Hillmen, P., et al. (2021). Pooled analysis of safety data from clinical trials evaluating acalabrutinib monotherapy in mature B-cell malignancies. *Leukemia* 35, 3201–3211. doi:10.1038/s41375-021-01252-y
- Ghia, P., Pluta, A., Wach, M., Lysak, D., Kozak, T., Simkovic, M., et al. (2020). ASCEND: phase III, randomized trial of acalabrutinib Versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *JCO* 38, 2849–2861. doi:10.1200/JCO.19.03355
- Gladman, D. D., Charles-Schoeman, C., McInnes, I. B., Veale, D. J., Thiers, B., Nurmohamed, M., et al. (2019). Changes in lipid levels and incidence of cardiovascular events following tofacitinib treatment in patients with psoriatic arthritis: a pooled analysis across phase III and long-term extension studies. *Arthritis Care Res. (Hoboken)* 71, 1387–1395. doi:10.1002/acr.23930
- Goess, C., Harris, C. M., Murdock, S., McCarthy, R. W., Sampson, E., Twomey, R., et al. (2019). ABBV-105, a selective and irreversible inhibitor of Bruton's tyrosine kinase, is efficacious in multiple preclinical models of inflammation. *Mod. Rheumatol.* 29, 510–522. doi:10.1080/14397595.2018.1484269
- Guha, A., Derbala, M. H., Zhao, Q., Wiczter, T. E., Woyach, J. A., Byrd, J. C., et al. (2018). Ventricular arrhythmias following ibrutinib initiation for lymphoid malignancies. *J. Am. Coll. Cardiol.* 72, 697–698. doi:10.1016/j.jacc.2018.06.002
- Gupta, S., Sharma, A., Shukla, A., Mishra, A., and Singh, A. (2025). From development to clinical success: the journey of established and next-generation BTK inhibitors. *Invest. New Drugs* 43, 377–393. doi:10.1007/s10637-025-01513-y
- Haselmayer, P., Camps, M., Liu-Bujalski, L., Nguyen, N., Morandi, F., Head, J., et al. (2019). Efficacy and pharmacodynamic modeling of the BTK inhibitor evobrutinib in autoimmune disease models. *J. Immunol.* 202, 2888–2906. doi:10.4049/jimmunol.1800583
- Herrmann, J. (2020). Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. *Nat. Rev. Cardiol.* 17, 474–502. doi:10.1038/s41569-020-0348-1
- Holopainen, T., Räsänen, M., Anisimov, A., Tuomainen, T., Zheng, W., Tvorogov, D., et al. (2015). Endothelial bmX tyrosine kinase activity is essential for myocardial hypertrophy and remodeling. *Proc. Natl. Acad. Sci. U.S.A.* 112, 13063–13068. doi:10.1073/pnas.1517810112
- Honigberg, L. A., Smith, A. M., Sirisawad, M., Verner, E., Loury, D., Chang, B., et al. (2010). The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc. Natl. Acad. Sci. U. S. A.* 107, 13075–13080. doi:10.1073/pnas.1004594107
- Hordinsky, M., Hebert, A. A., Gooderham, M., Kwon, O., Murashkin, N., Fang, H., et al. (2023). Efficacy and safety of ritlecitinib in adolescents with alopecia areata: results from the ALLEGRO phase 2b/3 randomized, double-blind, placebo-controlled trial. *Pediatr. Dermatol.* 40, 1003–1009. doi:10.1111/pde.15378
- Hsu, L.-Y., Rosenbaum, J. T., Verner, E., Jones, W. B., Hill, C. M., Janc, J. W., et al. (2024). Synthesis and characterization of soquelitinib a selective ITK inhibitor that modulates tumor immunity. *Npj Drug Discov.* 1, 2. doi:10.1038/s44386-024-00002-1

- Jebaraj, B. M. C., Müller, A., Dheenadayalan, R. P., Endres, S., Roessner, P. M., Seyfried, F., et al. (2022). Evaluation of vecabrutinib as a model for noncovalent BTK/ITK inhibition for treatment of chronic lymphocytic leukemia. *Blood* 139, 859–875. doi:10.1182/blood.2021011516
- Jiang, S., Jiang, T., Huang, H., Chen, X., Li, L., Wang, Z., et al. (2022). CHMFL-BMX-078, a BMX inhibitor, overcomes the resistance of melanoma to vemurafenib via inhibiting AKT pathway. *Chemico-Biological Interact.* 351, 109747. doi:10.1016/j.cbi.2021.109747
- Jiang, B., Weinstock, D. M., Donovan, K. A., Sun, H.-W., Wolfe, A., Amaka, S., et al. (2023). ITK degradation to block T-cell receptor signaling and overcome therapeutic resistance in T-Cell lymphomas. *Cell Chem. Biol.* 30, 383–393.e6. doi:10.1016/j.chembiol.2023.03.007
- Kashiwakura, J., Suzuki, N., Nagafuchi, H., Takeno, M., Takeba, Y., Shimoyama, Y., et al. (1999). Txk, a nonreceptor tyrosine kinase of the Tec family, is expressed in T helper type 1 cells and regulates interferon γ production in human T lymphocytes. *J. Exp. Med.* 190, 1147–1154. doi:10.1084/jem.190.8.1147
- Keam, S. J. (2023). Pirtobrutinib: first approval. *Drugs* 83, 547–553. doi:10.1007/s40265-023-01860-1
- Khountham, S., Shindiapina, P., Mo, X., Lachowicz, C., Wiczer, T., Mousa, L., et al. (2021). Natural history of noninfectious, ibrutinib-attributable adverse events in patients with chronic lymphocytic leukemia. *Leukemia and Lymphoma* 62, 716–721. doi:10.1080/10428194.2020.1838508
- King, B., Guttman-Yassky, E., Peeva, E., Banerjee, A., Sinclair, R., Pavel, A. B., et al. (2021). A phase 2a randomized, placebo-controlled study to evaluate the efficacy and safety of the oral janus kinase inhibitors ritlecitinib and breprocitinib in alopecia areata: 24-week results. *J. Am. Acad. Dermatology* 85, 379–387. doi:10.1016/j.jaad.2021.03.050
- King, B., Zhang, X., Harcha, W. G., Szepletowski, J. C., Shapiro, J., Lynde, C., et al. (2023). Efficacy and safety of ritlecitinib in adults and adolescents with alopecia areata: a randomised, double-blind, multicentre, phase 2b–3 trial. *Lancet* 401, 1518–1529. doi:10.1016/s0140-6736(23)00222-2
- King, B., Soung, J., Tziotzios, C., Rudnicka, L., Joly, P., Gooderham, M., et al. (2024). Integrated safety analysis of ritlecitinib, an oral JAK3/TEC family kinase inhibitor, for the treatment of alopecia areata from the ALLEGRO clinical trial program. *Am. J. Clin. Dermatol* 25, 299–314. doi:10.1007/s40257-024-00846-3
- Kluppel, M., Donoviel, D. B., Brunkow, M. E., Motro, B., and Bernstein, A. (1997). Embryonic and adult expression patterns of the tec tyrosine kinase gene suggest a role in megakaryocytopoiesis, blood vessel development, and melanogenesis. *Cell Growth Differ.* 8, 1249–1256. Available online at: <https://pubmed.ncbi.nlm.nih.gov/9419413/>.
- Kudinov, A., and Darbar, D., (2020). Deciphering the electrophysiological mechanisms for Ibrutinib-Induced ventricular arrhythmias. *JACC CardioOncology* 2, 630–631. doi:10.1016/j.jaccao.2020.10.001
- Langrish, C. L., Bradshaw, J. M., Francesco, M. R., Owens, T. D., Xing, Y., Shu, J., et al. (2021). Preclinical efficacy and anti-inflammatory mechanisms of action of the bruton tyrosine kinase inhibitor rilzabrutinib for immune-mediated disease. *J. Immunol.* 206, 1454–1468. doi:10.4049/jimmunol.2001130
- Lechner, K. S., Neurath, M. F., and Weigmann, B. (2020). Role of the IL-2 inducible tyrosine kinase ITK and its inhibitors in disease pathogenesis. *J. Mol. Med. Berl.* 98, 1385–1395. doi:10.1007/s00109-020-01958-z
- Liang, X., Lv, F., Wang, B., Yu, K., Wu, H., Qi, Z., et al. (2017). Discovery of 2-(3-Acrylamido-4-methylphenyl)amino)-N-(2-methyl-5-(3,4,5-trimethoxybenzamido)phenyl)-4-(methylamino)pyrimidine-5-carboxamide (CHMFL-BMX-078) as a highly potent and selective type II irreversible bone marrow kinase in the X chromosome (BMX) kinase inhibitor. *J. Med. Chem.* 60, 1793–1816. doi:10.1021/acs.jmedchem.6b01413
- Liao, C.-K., Liu, C.-J., Tan, T.-D., Wang, M.-C., Hsu, Y.-T., Liu, H.-L., et al. (2024). Real world evidence of tirabrutinib as a salvage treatment in patients with relapsed or refractory primary central nervous system lymphoma in Taiwan: a multicenter study. *Blood. 66th ASH Annu. Meet. Abstr.* 144, 5137. doi:10.1182/blood-2024-201386
- Lin, T.-A., McIntyre, K. W., Das, J., Liu, C., O'Day, K. D., Penhallow, B., et al. (2004). Selective itk inhibitors block T-Cell activation and murine lung inflammation. *Biochemistry* 43, 11056–11062. doi:10.1021/bi049428r
- Lin, E. V., Suresh, R. V., and Dispenza, M. C. (2024). Bruton's tyrosine kinase inhibition for the treatment of allergic disorders. *Ann. Allergy, Asthma and Immunol.* 133, 33–42. doi:10.1016/j.anai.2024.03.002
- Lipsky, A., and Lamanna, N. (2020). Managing toxicities of bruton tyrosine kinase inhibitors. *Hematology* 2020, 336–345. doi:10.1182/hematology.2020000118
- Liu, L., Paolo, J. D., Barbosa, J., Rong, H., Reif, K., and Wong, H. (2011). Antiarthritis effect of a novel Bruton's tyrosine kinase (BTK) inhibitor in rat collagen-induced arthritis and mechanism-based pharmacokinetic/pharmacodynamic modeling: relationships between inhibition of BTK phosphorylation and efficacy. *J. Pharmacol. Exp. Ther.* 338, 154–163. doi:10.1124/jpet.111.181545
- Liu, F., Zhang, X., Weisberg, E., Chen, S., Hur, W., Wu, H., et al. (2013). Discovery of a selective irreversible BMX inhibitor for prostate cancer. *ACS Chem. Biol.* 8, 1423–1428. doi:10.1021/cb4000629
- Liu, N., Rowley, B. R., Bull, C. O., Schneider, C., Haegerbarth, A., Schatz, C. A., et al. (2013). BAY 80-6946 is a highly selective intravenous PI3K inhibitor with potent p110 α and p110 δ activities in tumor cell lines and xenograft models. *Mol. Cancer Ther.* 12, 2319–2330. doi:10.1158/1535-7163.MCT-12-0993-T
- Lo, H. Y. (2010). Itk inhibitors: a patent review. *Expert Opin. Ther. Pat.* 20, 459–469. doi:10.1517/13543771003674409
- Lucas, J. A., Miller, A. T., Atherly, L. O., and Berg, L. J. (2003). The role of tec family kinases in T cell development and function. *Immunol. Rev.* 191, 119–138. doi:10.1034/j.1600-065X.2003.00029.x
- Maddocks, K. J., Ruppert, A. S., Lozanski, G., Heerema, N. A., Zhao, W., Abruzzo, L., et al. (2015). Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncol.* 1, 80–87. doi:10.1001/jamaoncol.2014.218
- Markham, A., and Dhillon, S. (2018). Acalabrutinib: first global approval. *Drugs* 78, 139–145. doi:10.1007/s40265-017-0852-8
- Marron, T. U., Martinez-Gallo, M., Yu, J. E., and Cunningham-Rundles, C. (2012). Toll-like receptor 4-7-and 8-activated myeloid cells from patients with X-linked agammaglobulinemia produce enhanced inflammatory cytokines. *J. Allergy Clin. Immunol.* 129, 184–190.e1–4. doi:10.1016/j.jaci.2011.10.009
- Mato, A. R., Nabhan, C., Thompson, M. C., Lamanna, N., Brander, D. M., Hill, B., et al. (2018). Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. *Haematologica* 103, 874–879. doi:10.3324/haematol.2017.182907
- Mato, A. R., Shah, N. N., Jurczak, W., Cheah, C. Y., Pagel, J. M., Woyach, J. A., et al. (2021). Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet* 397, 892–901. doi:10.1016/S0140-6736(21)00224-5
- McMullen, J. R., Boey, E. J. H., Ooi, J. Y. Y., Seymour, J. F., Keating, M. J., and Tam, C. S. (2014). Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. *Blood* 124, 3829–3830. doi:10.1182/blood-2014-10-604272
- Munir, T., Brown, J. R., O'Brien, S., Barrientos, J. C., Barr, P. M., Reddy, N. M., et al. (2019). Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am. J. Hematol.* 94, 1353–1363. doi:10.1002/ajh.25638
- Owen, R. G., McCarthy, H., Rule, S., D'Sa, S., Thomas, S. K., Tournilhac, O., et al. (2020). Acalabrutinib monotherapy in patients with waldenström macroglobulinemia: a single-arm, multicentre, phase 2 study. *Lancet Haematol.* 7, e112–e121. doi:10.1016/S2352-3026(19)30210-8
- Owens, T. D., Smith, P. F., Redfern, A., Xing, Y., Shu, J., Karr, D. E., et al. (2022). Phase 1 clinical trial evaluating safety, exposure and pharmacodynamics of BTK inhibitor tolebrutinib (PRN2246, SAR442168). *Clin. Transl. Sci.* 15, 442–450. doi:10.1111/cts.13162
- Pandey, A. K., Singhi, E. K., Arroyo, J. P., Ikizler, T. A., Gould, E. R., Brown, J., et al. (2018). Mechanisms of VEGF (vascular endothelial growth factor) inhibitor-associated hypertension and vascular disease. *Hypertension* 71, e1–e8. doi:10.1161/HYPERTENSIONAHA.117.10271
- Park, J. K., Byun, J.-Y., Park, J. A., Kim, Y.-Y., Lee, Y. J., Oh, J. I., et al. (2016). 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.* 18, 91. doi:10.1186/s13075-016-0988-z
- Pineda-Gayoso, R., Alomar, M., Lee, D. H., and Fradley, M. G. (2020). Cardiovascular toxicities of bruton's tyrosine kinase inhibitors. *Curr. Treat. Options Oncol.* 21, 67. doi:10.1007/s11864-020-00764-6
- Ping, L., Ding, N., Shi, Y., Feng, L., Li, J., Liu, Y., et al. (2017). The Bruton's tyrosine kinase inhibitor ibrutinib exerts immunomodulatory effects through regulation of tumor-infiltrating macrophages. *Oncotarget* 8, 39218–39229. doi:10.18632/oncotarget.16836
- Qi, S., Cao, J., Wu, T., Shi, C., Wang, J., Wang, B., et al. (2025). Discovery of IHMT-15130 as a highly potent irreversible BMX inhibitor for the treatment of myocardial hypertrophy and remodeling. *ACS Chem. Biol.* 20, 1181–1194. doi:10.1021/acscchembio.4c00875
- Qiu, L., Wang, F., Liu, S., and Chen, X.-L. (2014). Current understanding of tyrosine kinase BMX in inflammation and its inhibitors. *Burns Trauma* 2, 121–124. doi:10.4103/2321-3868.135483
- Quartermaine, C., Ghazi, S. M., Yasin, A., Awan, F. T., Fradley, M., Wiczer, T., et al. (2023). Cardiovascular toxicities of BTK inhibitors in chronic lymphocytic leukemia. *JACC CardioOncol* 5, 570–590. doi:10.1016/j.jaccao.2023.09.002
- Ribeiro, M. L., Reyes-Garau, D., Vinyoles, M., Profitós Pelejà, N., Santos, J. C., Armengol, M., et al. (2021). Antitumor activity of the novel BTK inhibitor TG-1701 is associated with disruption of ikaros signaling in patients with B-cell non-hodgkin lymphoma. *Clin. Cancer Res.* 27, 6591–6601. doi:10.1158/1078-0432.CCR-21-1067
- Rosenzweig, R., Gupta, S., Kumar, V., Gumina, R. J., and Bansal, S. S. (2021). Estrogenic bias in T-Lymphocyte biology: implications for cardiovascular disease. *Pharmacol. Res.* 170, 105606. doi:10.1016/j.phrs.2021.105606
- Rozkiewicz, D., Hermanowicz, J. M., Kwiatkowska, I., Krupa, A., and Pawlak, D. (2023). Bruton's tyrosine kinase inhibitors (BTKIs): review of preclinical studies and evaluation of clinical trials. *Molecules* 28, 2400. doi:10.3390/molecules28052400

- Sandborn, W. J., Danese, S., Leszczyszyn, J., Romatowski, J., Altintas, E., Peeva, E., et al. (2023). Oral ritlicitinib and brepocitinib for moderate-to-severe ulcerative colitis: results from a randomized, phase 2b study. *Clin. Gastroenterology Hepatology* 21, 2616–2628.e7. doi:10.1016/j.cgh.2022.12.029
- Schwarzlich, M. A., and Witzens-Harig, M. (2014). Ibrutinib. Recent results. *Cancer Res.* 201, 259–267. doi:10.1007/978-3-642-54490-3_17
- Shah, N. N., Wang, M., Roeker, L. E., Patel, K., Woyach, J. A., Wierda, W. G., et al. (2024). Pirtobrutinib monotherapy in bruton tyrosine kinase inhibitor-intolerant patients with B-cell malignancies: results of the phase I/II BRUIN trial. *Haematologica* 110, 92–102. doi:10.3324/haematol.2024.285754
- Shirley, M. (2022). Bruton tyrosine kinase inhibitors in B-Cell malignancies: their use and differential features. *Target Oncol.* 17, 69–84. doi:10.1007/s11523-021-00857-8
- Siveen, K. S., Prabhu, K. S., Achkar, I. W., Kuttikrishnan, S., Shyam, S., Khan, A. Q., et al. (2018). Role of non receptor tyrosine kinases in hematological malignances and its targeting by natural products. *Mol. Cancer* 17, 31. doi:10.1186/s12943-018-0788-y
- Song, Y., Zhou, K., Zou, D., Zhou, J., Hu, J., Yang, H., et al. (2020). Treatment of patients with relapsed or refractory mantle-cell lymphoma with zanubrutinib, a selective inhibitor of bruton's tyrosine kinase. *Clin. Cancer Res.* 26, 4216–4224. doi:10.1158/1078-0432.CCR-19-3703
- Sousa, B. B., de Almeida, C. R., Barahona, A. F., Lopes, R., Martins-Logrado, A., Cavaco, M., et al. (2022). Selective inhibition of bruton's tyrosine kinase by a designed covalent ligand leads to potent therapeutic efficacy in blood cancers relative to clinically used inhibitors. *ACS Pharmacol. Transl. Sci.* 5, 1156–1168. doi:10.1021/acspsci.2c00163
- Study to Evaluate Efficacy (2025). Safety and tolerability of JTE-051 in subjects with active rheumatoid arthritis. Available online at: <https://www.smartpatients.com/trials/NCT02919475> (Accessed 12 May 2025).
- Syed, Y. Y. (2020). Zanubrutinib: first approval. *Drugs* 80, 91–97. doi:10.1007/s40265-019-01252-4
- Tam, C. S., Opat, S., D'Sa, S., Jurczak, W., Lee, H.-P., Cull, G., et al. (2020). A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic waldenström macroglobulinemia: the ASPEN study. *Blood* 136, 2038–2050. doi:10.1182/blood.2020066844
- Telliez, J.-B., Dowty, M. E., Wang, L., Jussif, J., Lin, T., Li, L., et al. (2016). Discovery of a JAK3-Selective inhibitor: functional differentiation of JAK3-Selective inhibition over pan-JAK or JAK1-Selective inhibition. *ACS Chem. Biol.* 11, 3442–3451. doi:10.1021/acscchembio.6b00677
- Thorarensen, A., Dowty, M. E., Banker, M. E., Juba, B., Jussif, J., Lin, T., et al. (2017). Design of a janus kinase 3 (JAK3) specific inhibitor 1-((2S,5R)-5-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one (PF-06651600) allowing for the interrogation of JAK3 signaling in humans. *J. Med. Chem.* 60, 1971–1993. doi:10.1021/acscimedchem.6b01694
- Wang, M. L., Jurczak, W., Zinzani, P. L., Eyre, T. A., Cheah, C. Y., Ujjani, C. S., et al. (2023). Pirtobrutinib in covalent bruton tyrosine kinase inhibitor pretreated mantle-cell lymphoma. *J. Clin. Oncol.* 41, 3988–3997. doi:10.1200/JCO.23.00562
- Watterson, S. H., Liu, Q., Beaudoin Bertrand, M., Batt, D. G., Li, L., Pattoli, M. A., et al. (2019). Discovery of branebrutinib (BMS-986195): a strategy for identifying a highly potent and selective covalent inhibitor providing rapid *in vivo* inactivation of Bruton's tyrosine kinase (BTK). *J. Med. Chem.* 62, 3228–3250. doi:10.1021/acscimedchem.9b00167
- Wiczner, T. E., Levine, L. B., Brumbaugh, J., Coggins, J., Zhao, Q., Ruppert, A. S., et al. (2017). Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib. *Blood Adv.* 1, 1739–1748. doi:10.1182/bloodadvances.2017009720
- Woyach, J. A., Flinn, I. W., Awan, F. T., Eradat, H., Brander, D., Tees, M., et al. (2022). Efficacy and safety of nemtabrutinib, a wild-type and C481S-Mutated bruton tyrosine kinase inhibitor for B-Cell malignancies: updated analysis of the open-label phase 1/2 dose-expansion Bellwave-001 study. *Blood* 140, 7004–7006. doi:10.1182/blood-2022-163596
- Woyach, J. A., Stephens, D. M., Flinn, I. W., Bhat, S. A., Savage, R. E., Chai, F., et al. (2024). First-in-Human study of the reversible BTK inhibitor nemtabrutinib in patients with relapsed/refractory chronic lymphocytic leukemia and B-Cell non-hodgkin lymphoma. *Cancer Discov.* 14, 66–75. doi:10.1158/2159-8290.CD-23-0670
- Xiao, L., Salem, J.-E., Clauss, S., Hanley, A., Bapat, A., Hulsmans, M., et al. (2020). Ibrutinib-mediated atrial fibrillation attributable to inhibition of C-Terminal Src kinase. *Circulation* 142, 2443–2455. doi:10.1161/CIRCULATIONAHA.120.049210
- Xu, D., Kim, Y., Postelnek, J., Vu, M. D., Hu, D.-Q., Liao, C., et al. (2012). RN486, a selective Bruton's tyrosine kinase inhibitor, abrogates immune hypersensitivity responses and arthritis in rodents. *J. Pharmacol. Exp. Ther.* 341, 90–103. doi:10.1124/jpet.111.187740
- Xu, H., Jesson, M. I., Seneviratne, U. I., Lin, T. H., Sharif, M. N., Xue, L., et al. (2019). PF-06651600, a dual JAK3/TEC family kinase inhibitor. *ACS Chem. Biol.* 14, 1235–1242. doi:10.1021/acscchembio.9b00188
- Xu, W., Song, Y., Li, Z., Yang, S., Liu, L., Hu, Y., et al. (2019). Safety, tolerability and efficacy of orelabrutinib, once a day, to treat Chinese patients with relapsed or refractory chronic lymphocytic leukemia/small cell leukemia. *Blood* 134, 4319. doi:10.1182/blood-2019-123331
- Yang, W.-C., Ching, K. A., Tsoukas, C. D., and Berg, L. J. (2001). Tec kinase signaling in T cells is regulated by phosphatidylinositol 3-Kinase and the tec pleckstrin homology Domain1. *J. Immunol.* 166, 387–395. doi:10.4049/jimmunol.166.1.387
- Yin, Z., Zou, Y., Wang, D., Huang, X., Xiong, S., Cao, L., et al. (2022). Regulation of the tec family of non-receptor tyrosine kinases in cardiovascular disease. *Cell Death Discov.* 8, 119. doi:10.1038/s41420-022-00927-4
- Yu, L., and Smith, C. I. E. (2011). Tec family kinases. *FEBS J.* 278, 1969. doi:10.1111/j.1742-4658.2011.08135.x
- Zanubrutinib (2012). in *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* (Bethesda: National Institute of Diabetes and Digestive and Kidney Diseases).
- Zarrin, A. A., Bao, K., Lupardus, P., and Vucic, D. (2021). Kinase inhibition in autoimmunity and inflammation. *Nat. Rev. Drug Discov.* 20, 39–63. doi:10.1038/s41573-020-0082-8
- Zhang, B., Zhao, R., Liang, R., Gao, Y., Liu, R., Chen, X., et al. (2020). Abstract CT132: orelabrutinib, a potent and selective Bruton's tyrosine kinase inhibitor with superior safety profile and excellent PK/PD properties. *Cancer Res.* 80, CT132. doi:10.1158/1538-7445.AM2020-CT132
- Zhong, Y., Dong, S., Strattan, E., Ren, L., Butchar, J. P., Thornton, K., et al. (2015). Targeting Interleukin-2-inducible T-cell kinase (ITK) and resting lymphocyte kinase (RLK) using a novel covalent inhibitor PRN694. *J. Biol. Chem.* 290, 5960–5978. doi:10.1074/jbc.M114.614891