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Advancing BTK Inhibition: Non-Covalent Bruton Tyrosine Kinase Inhibitors and Their Emerging Role in Canadian Practice

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Introduction

The B-cell receptor (BCR) signaling pathway is a key driver in the development of B-cell malignancies, such as chronic lymphocytic leukemia (CLL), Waldenstrom's macroglobulinemia (WM), mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL), by promoting abnormal proliferation and survival.[1] Antigen binding to the BCR triggers activation of Bruton's tyrosine kinase (BTK), which in turn leads to activation of the nuclear factor kappa-B (NFκB) pathway, leading to nuclear translocation of NF-κB transcription factors.[1,2] The essential role of BTK activation in BCR signaling highlights the rationale for BTK inhibition as a targeted therapeutic intervention in B-cell malignancies, effectively suppressing BCR signaling and limiting B-cell proliferation and survival.

Covalent BTK Inhibitors

Numerous covalent BTK inhibitors (BTKi) including ibrutinib, acalabrutinib, and zanubrutinib are Health Canada approved for use in both the relapsed/refractory (R/R) and treatment-naïve settings in various B-cell lymphoma subtypes. These oral agents have notable and durable efficacy across a broad range of B-cell malignancies, transforming treatment paradigms by shifting the standard of care from traditional chemoimmunotherapy to targeted therapies.[3–6]

Covalent BTKis bind irreversibly to the cysteine 481 (C481) residue of BTK, blocking the adenosine triphosphate (ATP)-binding pocket and inhibiting autophosphorylation at tyrosine residue 223 (Y223), thereby preventing BTK's catalytic activity.[7] Despite their efficacy, resistance to covalent BTKis is frequently observed. Primary BTKi resistance is rare in CLL, and its underlying mechanisms remain poorly understood.[8] In contrast, primary resistance appears more frequent in MCL, observed in up to 30% of patients.[9]

Many patients with CLL and other B-cell malignancies eventually develop secondary, or acquired, resistance to BTKi therapy.[10] Several different resistance mechanisms have been described, however they vary by disease subtype, and the overall landscape remains incompletely understood. In CLL, two key resistance mechanisms have been identified in patients with disease progression on ibrutinib.[8,11,12] The most common is the C481S point mutation in BTK, which alters the cysteine binding site, preventing effective drug binding and thereby restoring catalytic activity of BTK. Additionally, gain-of-function mutations in phospholipase C gamma 2 (PCLG2) enable BCR signaling to continue independent of BTK.[11]

Mutations in BTK C481S have been linked to resistance across multiple B-cell malignancies and covalent BTK inhibitors. In CLL, early studies in multiply relapsed or refractory patients suggested a high rate of this mutation in up to 70–80% of patients who develop resistance to ibrutinib and acalabrutinib,[13] as well as in up to 40% of patients who develop Richter transformation while receiving ibrutinib.[10] More recent studies, however, have reported lower frequencies of BTK mutations than previously described, highlighting the fact that there are alternate resistance mechanisms still unaccounted for. For example, in the ELEVATE-RR trial, emergent BTK mutations were observed in 66% and 37% of patients progressing on acalabrutinib or ibrutinib respectively.[14] While

a recent publication of early progressors on the ALPINE trial (median follow-up 25.7 months) reported only 17% of patients with BTK mutations.[15] The C481S mutation has also been identified in ibrutinib-resistant WM[16] and in patients with MCL who progress during BTKi therapy.[17] In addition to BTK C481S mutations, in zanubrutinib-treated CLL patients, concurrent BTK L528W mutations have been observed, further reducing drug binding.[18] BTK L528W is a kinase-impaired mutation that reduces BTK's ability to undergo effective autophosphorylation. However, pre-clinical models have shown that these mutations have continued downstream signaling activity, possibly through the recruitment of alternative kinases.[19,20] Recent data among patients who progressed on acalabrutinib have demonstrated gatekeeper mutations in the T474 codon, generally co-occurring with BTK C481S mutations.[21] In contrast to L528W mutations, which were not seen among patients progressing on acalabrutinib,T474I mutations are kinase-proficient mutations, leading to increased autophosphorylation compared with wild-type BTK.[20,21] Beyond point mutations, other mechanisms of resistance to covalent BTKis in CLL and B-cell lymphomas include genomic and epigenetic alterations that lead to activation of downstream signaling pathways, such as the NFκB pathway.[22]

Non-covalent BTK Inhibitors

Mechanism of Action

Non-covalent BTK inhibitors differ significantly from covalent BTKis in both their structure and mechanism of action, offering an important therapeutic strategy to improve patient outcomes when covalent BTKis have failed (**Figure 1**). Unlike covalent BTKis, non-covalent BTKis do not bind to the C481 residue of BTK. Instead, they interact with BTK reversibly through a network of hydrogen bonds, ionic interactions, and hydrophobic forces.[23] These key differences allow non-covalent BTKis to retain efficacy in patients with C481S mutations and may also offer improved tolerability. As such, they represent a promising alternative for patients who have progressed on or are intolerant to covalent BTKis.

Based on available data, five non-covalent BTKis have entered clinical development. However, one of them, vecabrutinib, has not advanced beyond a phase 1 trial due to insufficient evidence of clinical activity, despite demonstrating a favourable safety profile.[24] Key characteristics of the remaining 4 non-covalent BTKis are summarized in **Table 1**, along with the status of their current clinical development and most recent published trials. Nemtabrutinib (MK-1026, formerly ARQ-531) binds to BTK by forming hydrogen bonds with residues E475 and Y476, while fenebrutinib forms hydrogen bonds with K430, M477, and D539.[25,26] Pirtobrutinib (LOXO-305) and docirbrutinib (AS-1763) act by reversibly occupying the ATP-binding site of BTK, thereby blocking its kinase activity.[23,27]

Pirtobrutinib in CLL/SLL

Pirtobrutinib is a reversible, oral BTK inhibitor with potent activity against both wild-type and C481S-mutated BTK.[28] Pirtobrutinib is highly selective for BTK, demonstrating over 300-fold selectivity for BTK compared to more than 98% of other kinases, suggesting a potential lower rate of off-target effects.[23] It has also been shown to enhance the stability of BTK in a closed, inactive form, in contrast to covalent BTKis which promote an open, active confirmation which may allow kinase-independent BTK cellular signaling. Pirtobrutinib has been designed to maintain greater than 90% of maximal BTK inhibition at trough levels, ensuring sustained target inhibition throughout the dosing interval.[23]

The phase 1-2 BRUIN trial is a multicentre dose-escalation and expansion study evaluating pirtobrutinib monotherapy in patients with previously treated B-cell malignancies, including CLL, Richter transformation, MCL, and other non-Hodgkin lymphomas (**Figure 2**).[28] Among the 773 patients with B-cell malignancies enrolled in the BRUIN trial, 317 had relapsed or refractory CLL or small lymphocytic lymphoma (SLL), of whom 247 had received prior BTKi therapy and were evaluated for efficacy. The median number of prior treatment lines was 3 and, notably, 41% of patients had also received a BCL2 inhibitor. Most patients (76%) discontinued prior BTKi therapy due to disease progression. High-risk molecular features were frequent and included deletion 17p, TP53 mutation, or both in 46.6% of patients, complex karyotype in 42%, and unmutated IGHV in 84.8%. Among the 222 patients with available pretreatment molecular data, 38% had a BTK C481 mutation and 8% had a PLCG2 mutation.[28]

Overall response rate (ORR) among patients previously treated with a covalent BTKi was 73.3%, which increased to 82.2% when partial response (PR) with lymphocytosis was included.[28]

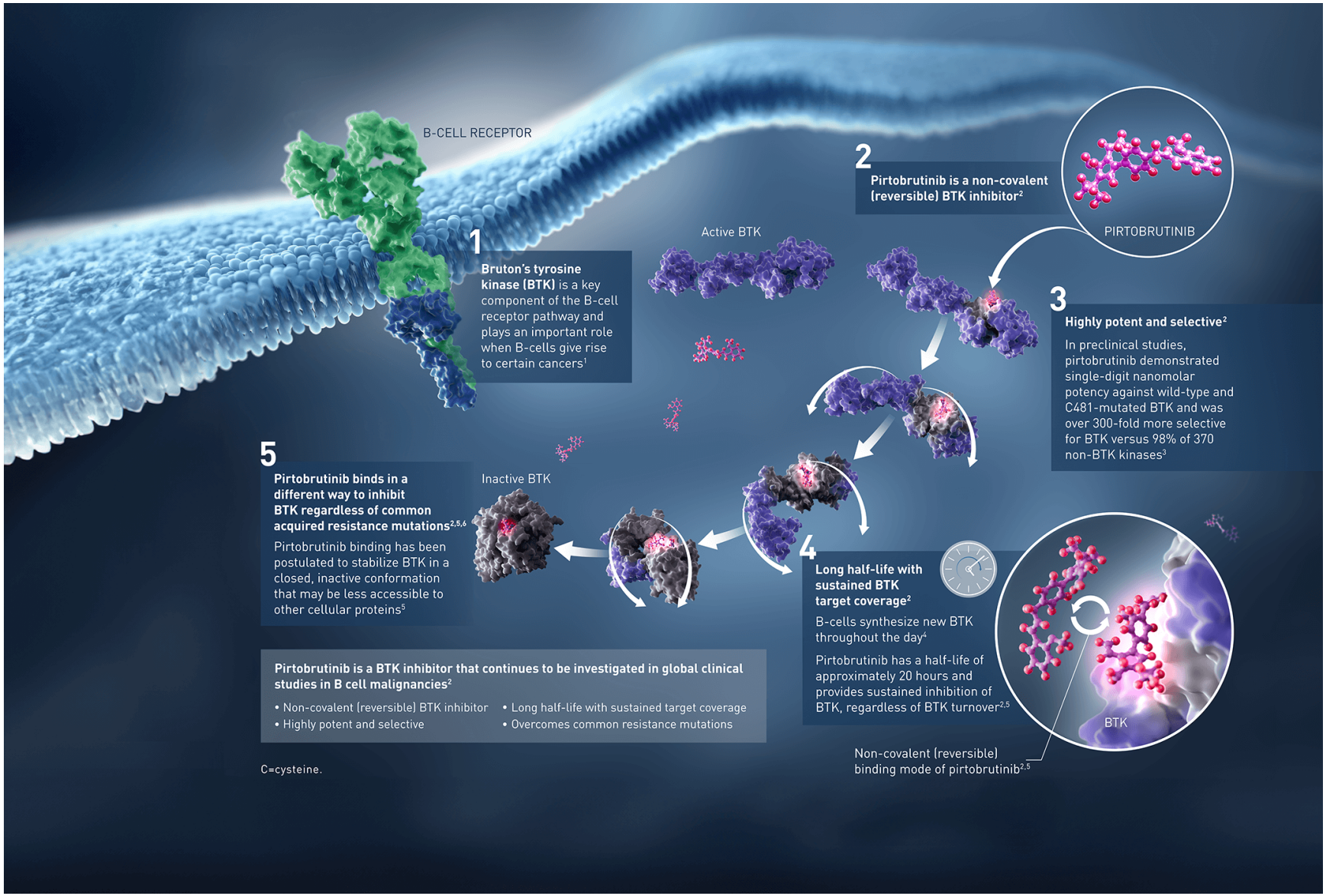


Figure 1. Mechanism of action of pirtobrutinib; *from Lilly Canada*.[65]

References: [67]Estupiñán HY, et al. *Front Cell Dev Biol.* 2021;9:630942; [68]Mato AR, et al. *Lancet*. 2021;397(10277):892-901; [69]Brandhuber B, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:S216; [70]Alsadhan A, et al. *Clin Cancer Res.* 2020;26(12):2800-2809; [71]Gomez EB, et al. *Blood*. 2023;142(1):62-72; [72]Gomez EB, et al. *Blood*. 2019;134(suppl 1):4644.

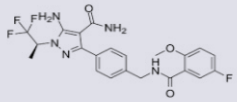
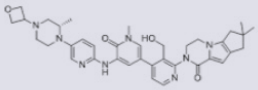
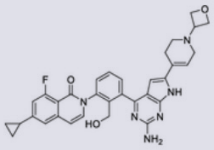
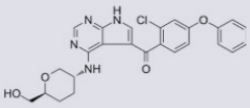
Non-covalent BTKi	Pirtobrutinib	Fenebrutinib	Docirbrutinib	Nemtabrutinib
Structure				
Binding to BTK	Blocks the ATP binding site of BTK	Hydrogen bonds with K430, M477, D539	Blocks the ATP binding site of BTK	Hydrogen bonds with E475, Y476
Other enzyme activity	Minimal	Minimal	Not reported	Activity on SRC, ERK, AKT. Inhibits signaling downstream to PCLG2.
Side effects (%)	Fatigue (20%) Diarrhea (17%) Neutropenia (13%)	Fatigue (37.7%) Nausea (33%) Diarrhea (29%) Thrombocytopenia (25%) Headache (21%)	Neutropenia (14%) ALT/AST elevation (7%)	Nausea (10%) Diarrhea (10%) Fatigue (8%) Neutropenia (8%) Dysgeusia (8%) Rash (8%)
Clinical development	Phase 1b/2 ongoing in B-cell malignancies Phase 3 ongoing in MCL and CLL	Terminated in B-cell malignancies	Phase 1b ongoing in B-cell malignancies	Phase 2 ongoing in B-cell malignancies
Key publications	28, 33, 35	25, 38	27, 40	36, 37

Table 1. Summary of characteristics of non-covalent BTK inhibitors in clinical development; *adapted from Lewis et al.*[66]

Abbreviations: BTK: Bruton's tyrosine kinase, **BTKi:** Bruton's tyrosine kinase inhibitor, **ATP:** adenosine triphosphate, **MCL:** mantle cell lymphoma, **CLL:** chronic lymphocytic leukemia.

The median progression-free survival (PFS) for the entire cohort was 19.6 months, and in patients previously treated with both a BTKi and a BCL2 inhibitor, the median PFS was 16.8 months. Similar PFS estimates were observed regardless of BTK C481 mutation status, patient age, or adverse cytogenetic and molecular features. Among patients with deletion 17p, median PFS was 16.9 months. At a median follow-up of 22.6 months, the estimated 12-month overall survival (OS) among patients previously treated with a BTKi was 86.0%.[28]

Among the 317 patients in the safety cohort, the most common adverse events were infections (71.0%), bleeding (42.6%), and neutropenia (32.5%). Any-grade hypertension was reported in 9.2% of patients, atrial fibrillation or flutter in 2.8%, and grade ≥3 hemorrhagic events were observed in 1.8% of patients. Importantly, no cases of drug-related ventricular arrhythmias/tachycardia or sudden cardiac death were reported. Overall, pirtobrutinib was well tolerated with treatment-related adverse events leading to dose reductions in 4.5% and permanent treatment discontinuation in 2.6%,[28] which is lower than historical discontinuation rates for cBTKis.[29,30] In a recent analysis of the BRUIN trial, none of the 127 patients who discontinued their prior BTKi due to intolerance (rather than disease progression) discontinued pirtobrutinib for the same adverse event.[31] Among those who discontinued their prior BTKi for a cardiac issue, 75% did not experience a recurrence of their cardiac event with pirtobrutinib.[31]

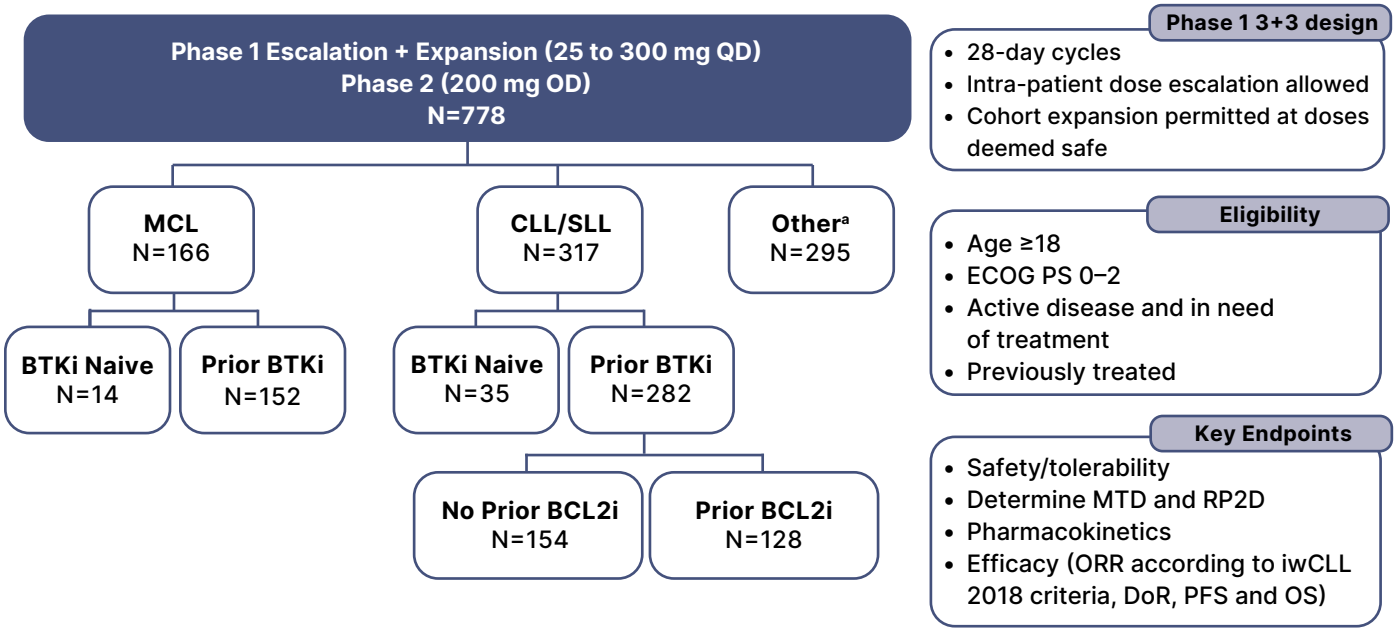


Figure 2. Phase 1–2 BRUIN trial CONSORT diagram; *adapted from Woyach et al.*[62]

[a]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformations.

Abbreviations: B-PLL: B cell prolymphocytic leukemia, **BTKi:** Bruton's tyrosine kinase inhibitor, **CLL:** chronic lymphocytic leukemia, **DLBCL:** diffuse large B cell lymphoma, **DOR:** duration of response, **ECOG PS:** Eastern Cooperative Oncology Group performance score, **FL:** follicular lymphoma, **MCL:** mantle cell lymphoma; **MTD:** maximum tolerated dose, **RP2D:** recommended Phase 2 dose, **ORR:** overall response rate, **OS:** overall survival, **PCNSL:** primary central nervous system lymphoma, **PFS:** progression-free survival, **SLL:** small lymphocytic lymphoma, **WM:** Waldenstrom's macroglobulinemia.

The phase 1-2 BRUIN trial demonstrated that pirtobrutinib has efficacy in patients with CLL/SLL who have previously received a BTKi, suggesting that CLL/SLL maintains dependency on BCR signaling mediated by BTK, despite previous exposure to a covalent BTKi. Pirtobrutinib was safe and well-tolerated, including among patients with prior BTKi-intolerance, with low rates of atrial fibrillation, major hemorrhage, or hypertension overall and low rates of treatment discontinuation.

The BRUIN study also evaluated pirtobrutinib in 82 patients with Richter transformation, of whom 90% of patients had received at least one prior treatment directed at Richter transformation and 74% had previously been treated with a covalent BTKi.[32] The ORR was 50% (13% complete responses, 37% PR) and the median duration of response was 7.4 months. Median PFS and OS were 4.9 months and 12.5 months, respectively.[32] These findings demonstrate promising efficacy of pirtobrutinib in patients with Richter transformation, including those previously treated with covalent BTKis.

The phase 1-2 BRUIN trial paved the way for a randomized, open-label, phase 3 study (BRUIN CLL-321) evaluating pirtobrutinib versus investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) in patients with relapsed or refractory CLL/SLL previously treated with a covalent BTKi, with preliminary results on 238 patients recently presented.[33] Baseline characteristics were well balanced and reflected a poor prognosis cohort, with 54% of patients exhibiting high-risk cytogenetics with deletion 17p and/or *TP53* mutation, and 33% having received at least 4 prior lines of therapy, including 50% who had been treated with a BCL2 inhibitor.[33] After a median

follow-up of 19.4 months, median PFS was 14.0 months with pirtobrutinib versus 8.7 months with IdelaR/BR, with the benefit sustained across clinical subgroups. Time to next treatment or death (TTNT) was 24.0 months with pirtobrutinib vs. 10.9 months with IdelaR/BR; TTNT was longer with pirtobrutinib in venetoclax-naïve patients at 29.5 months compared to 20.0 months in those with prior venetoclax exposure. Overall survival was not significantly different at the time of analysis, with high rates of crossover to pirtobrutinib (76%) in the control arm for patients with progressive disease. Consistent with the findings in the phase 1-2 BRUIN trial, pirtobrutinib was well tolerated with only 5% discontinuing treatment due to adverse events.[33]

Pirtobrutinib is also being evaluated in the first-line setting in CLL/SLL patients in a fixed-duration triplet combination with venetoclax and obinutuzumab (PVO).[34] Early results with a median follow-up of 11.9 months demonstrate high rates of undetectable minimal residual disease (MRD) in the bone marrow at 6 and 12 months of 64% and 80%, respectively.[34] These preliminary results are encouraging and may support the future use of fixed-duration, combination treatments with pirtobrutinib in newly diagnosed CLL, however further follow-up is required. Pirtobrutinib is currently being further investigated in patients with CLL/SLL in three additional global phase 3 trials, both in the upfront and relapsed settings, as monotherapy and in combination with other agents. **Table 2** highlights these pivotal studies, along with selected phase 2 combination trials.

Pirtobrutinib in MCL

Covalent BTKis have dramatically changed the treatment landscape of MCL, however patients continue to relapse due to intolerance or drug resistance. BTK mutations in C481, well described in CLL/SLL patients on covalent BTKis, are uncommon in MCL. Resistance mechanisms in MCL are not well understood but may include epigenetic or genetic mechanisms that restore BTK signaling,[8] or there may be increased BTK protein turnover as the neoplastic MCL cells become more proliferative over time, thereby leading to incomplete target inhibition with covalent BTKis.[35] Studies have demonstrated that patients with MCL who progress after covalent BTKi therapy have very poor outcomes, with median OS reported <10 months.[35] Although CD19-targeted chimeric antigen receptor (CAR) T-cell therapy is now Health Canada approved for relapsed/refractory MCL after at least 2 prior lines of therapy including a BTKi, not all patients are eligible. Therefore, there remains an unmet clinical need for effective and better tolerated MCL therapies after covalent BTKis.

The phase 1-2 BRUIN trial included 164 patients with MCL, of whom 90 were previously treated with a covalent BTKi.[35] Patients received a median of 3 prior lines of therapy and 82.2% discontinued their previous BTKi because of disease progression. The ORR in this cohort was 57.8% and, at a median follow-up of 12 months, the median duration of response was 21.6 months. The most common adverse events were fatigue (29.9%), diarrhea (21.3%), and dyspnea (16.5%), and grade ≥3 adverse events were infrequent, including hemorrhage (3.7%) and atrial fibrillation/flutter (1.2%). Only 3% of patients discontinued pirtobrutinib due to treatment-related adverse events. After treatment with pirtobrutinib, 18.9% of patients subsequently received CAR T-cell therapy.[35]

The encouraging efficacy and safety results from the MCL cohort of the phase 1–2 BRUIN study led to the initiation of a multicentre randomized, phase 3 clinical trial (BRUIN MCL-321) evaluating pirtobrutinib vs. investigator's choice of covalent BTKi in the relapsed/refractory setting, which will provide highly anticipated information on a direct comparison between non-covalent and covalent BTKis. This trial, along with selected phase 2 clinical trials of pirtobrutinib in combination with other agents for MCL, are detailed in **Table 2**.

Nemtabrutinib

Another reversible non-covalent BTKi is nemtabrutinib (MK-1026, formally known as ARQ-531). Similar to other agents in this class, it inhibits both wild-type BTK and C481-mutant BTK.[26] This is achieved through the formation of hydrogen bonds with the E475 and Y476 residues within the BTK kinase domain. However, unlike more selective non-covalent BTKis, nemtabrutinib has broader kinase activity, also inhibiting off-target kinases such as SRC, AKT, and ERK. This wider kinase profile may contribute to its anti-proliferative activity observed across multiple hematologic malignancies in pre-clinical studies.[26]

A phase 1 dose-escalation trial of nemtabrutinib showed clinical activity in CLL patients including those who harbored C481 and PLCG2 mutations, as well as patients with other B-cell non-Hodgkin lymphomas including Richter transformation.[36]

Trial	Phase	Population	Experimental arm	Control arm
Pirtobrutinib – CLL				
BRUIN CLL-313 (NCT05023980)	3	Treatment-naïve CLL/SLL	Pirtobrutinib	Bendamustine + Rituximab
BRUIN-CLL-314 (NCT05254743)	3	Treatment-naïve and R/R CLL/SLL	Pirtobrutinib	Ibrutinib
BRUIN CLL-322 (NCT04965493)	3	R/R CLL/SLL	Pirtobrutinib + Venetoclax + Rituximab	Venetoclax + Rituximab
NCT06333262	2	Treatment-naïve CLL/SLL	Pirtobrutinib + Obinutuzumab	None
NCT04623541	2	Treatment-naïve CLL/SLL	Pirtobrutinib + Venetoclax	None
NCT06466122	2	R/R CLL/SLL resistant to covalent BTKi	Pirtobrutinib + Venetoclax	None
NCT06812715	2	R/R CLL after previous zanubrutinib	Pirtobrutinib	None
NCT06839872	2	R/R CLL/SLL after 1L acalabrutinib	Pirtobrutinib	None
Pirtobrutinib – MCL				
BRUIN MCL-321 (NCT04662255)	3	R/R MCL, BTKi naïve	Pirtobrutinib	Investigator's choice of covalent BTKi
NCT06263491	2	Treatment-naïve low risk MCL	Pirtobrutinib + Rituximab	None
GATE1 (NCT06522386)	2	Treatment-naïve MCL	Pirtobrutinib + Venetolax + Rituximab	None
NCT05529069	2	R/R MCL	Pirtobrutinib + Venetoclax	None
NCT06553872	2	R/R MCL	Pirtobrutinib + Brexucabtagene autoleucel	None
NCT05833763	2	R/R MCL after covalent BTKi exposure	Pirtobrutinib + Glofitamab	None
NCT06252675	2	R/R MCL	Pirtobrutinib + Glofitamab	None
Nemtabrutinib – CLL and Richter Transformation				
BELLWAVE-011 (NCT06136559)	3	Treatment-naïve CLL/SLL	Nemtabrutinib	Investigator's choice of Ibrutinib or Acalabrutinib
BELLWAVE-008 (NCT05624554)	3	Treatment-naïve CLL/SLL	Nemtabrutinib	CIT
BELLWAVE-010 (NCT05947851)	3	R/R CLL/SLL	Nemtabrutinib + Venetoclax	Venetoclax + Rituximab
NCT06863402	2	Richter transformation	Nemtabrutinib + Pembrolizumab	None
NCT05458297	2	Richter transformation	Nemtabrutinib + Zilovertamab vedotin	None

Table 2. Ongoing phase 3 and selected phase 2 clinical trials with non-covalent BTK inhibitors; f*rom ClinicalTrials.gov*.*
*Accessed March 28, 2025.

Abbreviations: BTKi: Bruton tyrosine kinase inhibitor, **CLL/SLL:** chronic lymphocytic leukemia/small lymphocytic lymphoma, **1L:** first-line, **MCL:** mantle cell lymphoma, **CIT:** chemoimmunotherapy.

Nemtabrutinib demonstrated safety and preliminary efficacy, with CLL/SLL patients achieving an ORR of 75% at the recommended phase 2 dose of 65 mg daily.

The BELLWAVE-001 trial is an ongoing phase 1–2 study evaluating nemtabrutinib in patients with relapsed or refractory B-cell malignancies, including CLL/SLL and initial results have demonstrated promising antitumor activity.[37] Of 112 patients enrolled, 57 had CLL/SLL with a median number of prior therapies of 4, prior BTKi in 95%, and prior BTKi and BCL2 inhibitor in 42%. High-risk features were common, with 63% having a BTK C481S mutation, 32% *TP53* mutation, and 33% deletion 17p. The ORR among CLL/SLL patients was 56%, with a median duration of response of 24.4 months and PFS of 26.3 months.[37]

Among all 112 patients with B-cell malignancies evaluated for safety, the most common adverse events of any grade included hypertension (30%), dysgeusia (21%), decreased neutrophils (20%), and arthralgias (20%). The discontinuation rate due to adverse events was 13%.[37] Based on these promising results, nemtabrutinib is being further explored in three global phase 3 trials in patients with CLL/SLL, both in the treatment-naïve and relapsed/refractory settings as monotherapy and in combination with other targeted agents (**Table 2**).

Other Non-covalent BTK Inhibitors

Vecabrutinib and fenebrutinib (GDC-0853) are both non-covalent BTKis which have shown clinical activity in phase 1 trials for relapsed/refractory CLL/SLL and other B-cell malignancies.[24,38] However, development of vecabrutinib was discontinued due to limited efficacy, while fenebrutinib is no longer being pursued for B-cell malignancies and is now under investigation for autoimmune diseases such as multiple sclerosis and systemic lupus erythematous.[39]

Docirbrutinib (AS-1763) is a novel, highly selective non-covalent BTKi that was shown to have *in vitro* activity against emerging covalent and non-covalent BTK resistance mutations (C481S, T474x, L528x).[27] Preliminary results from a phase 1b study of docirbrutinib in patients with B-cell malignancies who received at least 2 prior lines of therapy, including a covalent BTKi, demonstrated encouraging safety data with no drug-related atrial fibrillation or bleeding, nor treatment discontinuation among 14 patients, with the maximum tolerated dose not yet reached. Nine patients were included with relapsed/refractory CLL/SLL with a median of 4 median prior lines of therapy, and of those, 5 patients achieved a PR/PR with lymphocytosis.[40] The drug is now being evaluated in an expansion portion to determine the recommended phase 2 dose.

Rocbrutinib (LP-168) is a next-generation, selective BTK inhibitor designed to overcome resistance in CLL by targeting both wild-type BTK and key resistance mutations. It binds irreversibly to wild-type BTK and reversibly to C481 mutations (C481S, C481F, C481R), while also irreversibly inhibiting non-C481 mutations, including the gatekeeper mutation T474I.[41] As such, it has features of both covalent and non-covalent BTKis. In a Phase 1 study, 50 patients with relapsed or refractory B-cell malignancies were enrolled and evaluable for dose-limiting toxicities, including 47 patients with CLL. After a median follow up of 13.9 months, rocbrutinib demonstrated a promising ORR of 77.8%. The treatment is well tolerated with no dose-limiting toxicities.[41]

Mechanisms of Resistance to Non-covalent BTK Inhibitors

Despite the promising efficacy of non-covalent BTKis, disease progression has been observed in some patients during treatment, indicating that acquired resistance can occur. Recent studies investigating mechanisms of resistance have identified novel mutations in BTK and PLCG2 that appear to confer resistance to non-covalent BTKis. In the first report of 9 patients with relapsed/refractory CLL treated with pirtobrutinib on the BRUIN trial who subsequently discontinued therapy due to disease progression, newly identified BTK mutations associated with resistance to pirtobrutinib were identified.[42] These included kinase-impaired L528W, V416L, M437R and A428D mutations, and gatekeeper T474I mutations. Despite diminished BTK activation, authors showed sustained downstream activation of AKT, ERK, and hyperactivated calcium release even in the presence of the BTKi, indicating persistent downstream BCR signaling despite ongoing drug treatment.[42] Other groups described additional mutations causing the same pattern of inactive BTK.[43]

Further analysis of the entire BRUIN cohort identified 86 CLL/SLL patients who experienced disease progression while on pirtobrutinib.[44] At progression, 69% of patients acquired at least one new mutation, including BTK mutations in 44%. These included gatekeeper T474X

mutations (49%), kinase-impaired mutations at L528W (25%), C481S/R/Y mutations (12%) and additional alterations near the ATP-binding pocket (e.g., V416L, A428D, Y545N, D539 variants).[44] Furthermore, non-BTK mutations were observed in 52% of patients, including new mutations in *TP53* (14%), PLCG2 (7%), PIK3CA (7%), and BCL2 (3%). Interestingly, some BTK mutations detected at progression were present at low variant allele frequencies (1–4%) in baseline samples, suggesting pre-existing subclonal populations that expanded under pirtobrutinib pressure.[44] Of note, 29% of patients who progressed on pirtobrutinib had no detectable mutation by next-generation sequencing, illustrating that the driver for a substantial proportion of patients progressing on pirtobrutinib remains unknown. These findings reflect complex genomic evolution under selective pressure from BTK inhibitors and support the need for continued molecular monitoring to understand and address emerging resistance mechanisms.

Non-covalent BTK Inhibitors in the Canadian Treatment Landscape

Given their distinct mechanism of action, non-covalent BTKis are emerging as a promising option in the Canadian treatment landscape for CLL/SLL and other B-cell malignancies. Currently, front-line treatment for CLL/SLL in Canada includes either a time-limited approach with the combination of venetoclax-obinutuzumab or continuous covalent BTKi therapy, both supported by long-term data comparing their efficacy and safety to historical chemoimmunotherapy regimens.[4,5,45,46] Emerging evidence also supports combining covalent BTKis with BCL2 inhibitors in the front-line setting,[47-49] with the fixed-duration ibrutinib-venetoclax combination now Health Canada approved and progressing through provincial and territorial reimbursement pathways. These combination approaches are also used at first relapse, resulting in a growing population of patients who are double exposed and often double refractory, particularly by the third line of treatment and increasingly by the second line. This group represents a significant unmet clinical need in CLL, as historical data highlight the poor prognosis associated with this scenario.[50]

Non-covalent BTKis hold the promise to address this unmet need. Among them, pirtobrutinib is the most advanced in development, followed by nemtabrutinib. Pirtobrutinib was approved by the U.S. Food and Drug Administration (FDA) in December 2023 for adult patients with CLL/SLL who have received at least 2 prior lines of therapy, including both a BTKi and BCL2 inhibitor. Health Canada approval is awaited. When comparing historical PFS for this population of double exposed patients, pirtobrutinib appears to double the ORR and PFS.[28,50]

More intriguing is whether pirtobrutinib will be moved into earlier lines of therapy and perhaps into the front line. The BRUIN-321 trial of pirtobrutinib for relapsed/refractory CLL/SLL after BTKi includes 50% of patients who were venetoclax-naïve, and the median PFS was significantly improved over chemoimmunotherapy, paving the way for use of pirtobrutinib after covalent BTKis. Pirtobrutinib is also being evaluated in combination with venetoclax and rituximab in the relapsed/refractory setting in patients both with and without prior BTKi exposure (BRUIN-CLL 322).[51] The BRUIN-CLL 314 trial is exploring pirtobrutinib versus ibrutinib in previously untreated CLL/SLL patients,[52] the results of which will provide important efficacy and safety data regarding non-covalent BTKis in the first-line setting.

Even if these trials favour the early use of non-covalent BTKis, there remain many unanswered questions regarding optimal sequencing of BTKis due to the potential for cross-resistance between second-generation covalent and non-covalent BTKis. This has been demonstrated with acquired BTK L258W mutations in patients who progress on pirtobrutinib that have also been reported in patients who develop resistance on zanubrutinib, and with T474I gatekeeper mutations which have been demonstrated in cases of acalabrutinib resistance.[13,42] There is a lack of prospective data to accurately determine the clinical impact of these mutations, however, with case reports demonstrating clinical benefit of pirtobrutinib in patients with BTK L258W and T474I mutations.[53,54] The complexity and evolving understanding of mutational resistance patterns with BTKis highlight the urgent need for next-generation sequencing panels to assess and report variant BTK mutations (i.e., mutations outside of C481). Further studies of resistance and treatment sequencing are ongoing to identify the optimal sequencing of covalent and non-covalent BTKis, as well as their mechanisms of resistance and cross-resistance (**Table 2**).

In MCL, covalent BTKis are currently approved by Health Canada in the relapsed/refractory setting and funded in most jurisdictions. With the emerging

data suggesting improved results with the addition of covalent BTKis to chemoimmunotherapy in the first-line treatment of newly diagnosed transplant eligible and ineligible MCL patients,[9,55] it would be expected that by the time patients progress to second line, most patients will be either covalent BTKi exposed or resistant. For this population of patients, CD19-directed CAR T-cell therapy provides the best outcomes, with the latest updates showing a promising median PFS of 25.8 months and median OS of 46.6 months.[56]

Patients with MCL who relapse after CAR T-cell therapy, or who progress on covalent BTKis but require bridging therapy or who are not candidates for CAR T-cell therapy, remain an unmet clinical need in the treatment landscape of MCL. Based on data from the BRUIN trial, pirtobrutinib was approved by the U.S. FDA in January 2023 for relapsed/refractory MCL after at least 2 lines of systemic therapy, including a BTKi.[57] It was also granted conditional marketing authorization by the European Medicines Agency (EMA) in October 2023 for this same indication.[58] It has not yet been Health Canada approved, however the U.S. and European Union approvals underscore pirtobrutinib's role as a significant therapeutic option for patients with MCL, particularly those who have exhausted other treatments. Further trials are needed in these settings to confirm benefit and are ongoing. Pirtobrutinib is also currently being studied as a second line option for previously treated MCL patients who have not been exposed to BTKi versus ibrutinib or acalabrutinib in the BRUIN MCL-321 trial (**Table 2**).[59]

Treatment After Non-covalent BTKis – The Not-So-Distant Therapeutic Challenge

Non-covalent BTKis have redefined treatment options for patients with B-cell malignancies, particularly those who have been exposed to both covalent BTKis and BCL2 inhibitors. As their clinical use broadens however, a new challenge has already emerged: how to effectively manage disease progression following BTKi therapy. Encouragingly, there are ongoing clinical trials of several different classes of agents that may hold promise after non-covalent BTKi discontinuation. BTK protein degraders are in development which have demonstrated preclinical activity in *in vitro* models with variant BTK mutations,[20] and clinical activity in patients with relapsed/refractory CLL, including those with variant BTK mutations.[60,61] Additional therapeutic strategies under investigation include bispecific antibody therapies, PKCβ inhibitors and CAR T-cell therapies.[62-64] Another strategy is to combine non-covalent BTKis with other targeted agents in fixed-duration regimens, which may prevent or delay the emergence of BTK mutations. Notably, in the first-line setting, the fixed-duration combination of ibrutinib and venetoclax resulted in no detectable BTK mutations among 40 patients evaluated at time of CLL progression.[47] This strategy of combination therapy is being explored in a number of ongoing clinical trials (select trials listed in **Table 2**), highlighting a growing focus on both optimizing efficacy and minimizing resistance.

Conclusions

Non-covalent BTKis represent a significant advancement in the therapeutic landscape of B-cell malignancies, particularly for patients previously treated with covalent BTKis and BCL2-targeted therapies where applicable. As regulatory approval in Canada is anticipated, these agents are well-positioned to address an important clinical need among double-exposed and treatment-refractory patient populations. The emergence of resistance mutations, including those associated with possible cross-resistance between covalent and non-covalent BTKis, underscores the need for prospective clinical trials to assess the clinical impact of these mutations and to evaluate optimal treatment sequencing. Continued investigation into combination regimens, fixed-duration strategies, and novel therapeutic classes such as BTK degraders and bispecific antibodies will be critical to extending disease control. As these innovations are integrated into Canadian practice, they offer the potential to significantly improve patient outcomes and quality of life across the spectrum of B-cell malignancies.

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