

# Bruton tyrosine kinase inhibitors for the frontline treatment of chronic lymphocytic leukemia

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## ABSTRACT

Chronic lymphocytic leukemia (CLL) is the most commonly diagnosed adult leukemia in Canada. Biologic heterogeneity of CLL between patients results in variable disease trajectories and responses to therapy. Notably, compared with patients lacking high-risk features, those with such features—such as deletions in chromosome 17p, aberrations in the *TP53* gene, or unmutated immunoglobulin heavy chain variable region genes—experience inferior outcomes and responses to standard chemoimmunotherapy. Novel agents that target the B cell receptor signalling pathway, such as Bruton tyrosine kinase (BTK) inhibitors, have demonstrated clinical efficacy and safety in patients with treatment-naïve CLL, particularly those with high-risk features. However, given the current lack of head-to-head trials comparing BTK inhibitors, selection of the optimal BTK inhibitor for patients with CLL is unclear and requires consideration of multiple factors. In the present review, we focus on the efficacy, safety, and pharmacologic features of the BTK inhibitors that are approved or under clinical development, and we discuss the practical considerations for the use of those agents in the Canadian treatment landscape.

**Key Words** Bruton tyrosine kinase inhibitors, chronic lymphocytic leukemia, untreated disease, frontline therapy, first-line therapy

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## INTRODUCTION

Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of CD5-positive monoclonal B lymphocytes in peripheral blood, bone marrow, and lymphoid tissues<sup>1</sup>. It is the most commonly diagnosed adult leukemia in Canada, and it occurs predominantly in individuals 65 years of age and older<sup>2</sup>.

Although CLL is considered an indolent malignancy, its biologic heterogeneity results in variable disease trajectories and responses to therapy. For example, chemoimmunotherapy regimens—such as fludarabine–cyclophosphamide–rituximab (FCR—for young and fit patients), bendamustine–rituximab (BR—for older patients), and chlorambucil–obinutuzumab (for unfit patients)—produce good outcomes in patients with mutated immunoglobulin heavy chain variable region (*IGHV*) genes without chromosome 17p deletions [del(17p)]<sup>3–6</sup>. However, patients with high-risk features, such as the presence of del(17p), *TP53* aberrations, or unmutated *IGHV* experience less favourable outcomes with chemoimmunotherapy<sup>7–10</sup>.

Since the start of the 2000s, the development of targeted therapy, which, compared with chemoimmunotherapy, demonstrates improved efficacy in patients with high-risk features, has been paradigm-changing<sup>11</sup>. The new agents target the B cell receptor signalling pathway, whose dysregulation plays a critical role in disease pathogenesis<sup>12</sup>, and Bcl-2, an antiapoptotic protein frequently overexpressed in B cell malignancies<sup>13,14</sup>. Currently in Canada, novel agents approved for use in both treatment-naïve and relapsed CLL include the Bruton tyrosine kinase (BTK) inhibitors ibrutinib and acalabrutinib and the Bcl-2 inhibitor venetoclax; the PI3K inhibitor idelalisib is indicated only in the relapsed setting<sup>14–17</sup>.

Bruton tyrosine kinase is a Tec family protein kinase that functions downstream of the B cell receptor signalling pathway to help regulate B cell proliferation, maturation, differentiation, migration, and apoptosis<sup>18</sup>. Bruton tyrosine kinase is also expressed in other hematopoietic cells across all lineages, with the exception of T lymphocytes and plasma cells<sup>19</sup>; it is frequently overexpressed and constitutively activated in CLL cells<sup>20</sup>.

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The efficacy and safety of ibrutinib and acalabrutinib in treatment-naïve CLL have been validated in clinical trials, leading to Health Canada approval of those agents<sup>15,16</sup>. Based on improved progression-free survival (PFS) and overall survival (OS) in a comparison with chlorambucil (RESONATE-2 study), ibrutinib was first approved in July 2016 as monotherapy for use in treatment-naïve CLL<sup>21</sup>. In November 2019, based on results from the ILLUMINATE trial, in which ibrutinib–obinutuzumab, compared with chlorambucil–obinutuzumab, was associated with improved PFS, ibrutinib was granted an additional indication, in combination with obinutuzumab, for first-line CLL<sup>8</sup>.

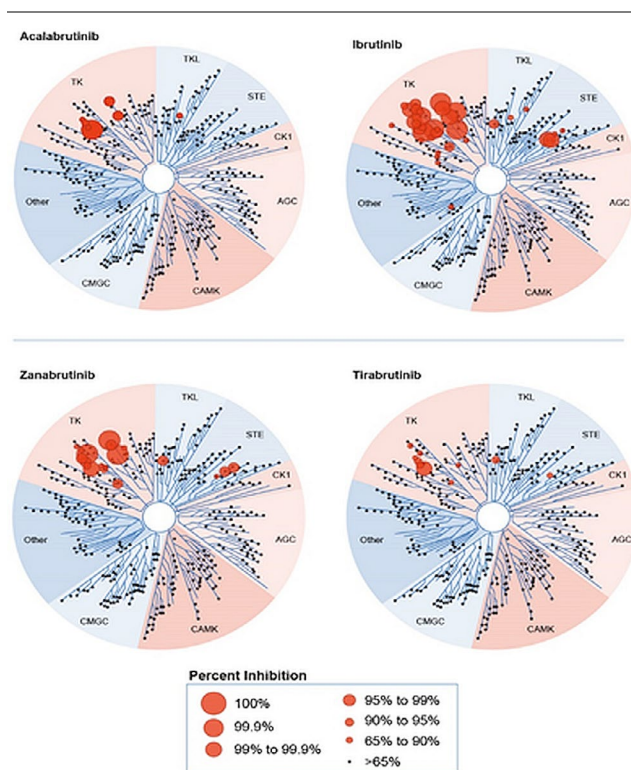
Acalabrutinib also gained Health Canada approval in November 2019 both as monotherapy and in combination with obinutuzumab for treatment-naïve CLL. Those approvals were based on results from the ELEVATE-TN trial, in which a PFS improvement was associated with acalabrutinib and acalabrutinib–obinutuzumab compared with chlorambucil–obinutuzumab in patients with treatment-naïve CLL<sup>10</sup>. The approvals were part of project Orbis, a collaborative effort between Health Canada, the U.S. Food and Drug Administration, and the Australian Therapeutic Goods Administration to simultaneously review new drug and medical device submissions, with the intent of granting patients earlier access to needed treatments<sup>22</sup>.

With the current lack of results from head-to-head trials comparing novel agents within this class, choosing the optimal BTK inhibitor-based regimen relies on careful consideration of efficacy and safety results from individual studies, as well as on practical factors. The present review focuses on the efficacy, safety, and pharmacologic features of the BTK inhibitors currently approved in Canada, as well as those in clinical development, and discusses practical considerations for the use of those agents in the Canadian treatment landscape.

## DISCUSSION

### BTK Inhibitor Selectivity and Pharmacodynamics Irreversible Covalent Inhibitors

Ibrutinib, acalabrutinib, zanubrutinib, and tirabrutinib are orally bioavailable, irreversible BTK inhibitors approved for use or under investigation in CLL. They function by covalently binding the C481 residue in the ATP binding domain of BTK<sup>23,24</sup> (Figure 1, Table 1). The first-in-class BTK inhibitor ibrutinib demonstrated potent inhibition of BTK<sup>25</sup>; however, *in vitro* studies demonstrate low selectivity for BTK, with off-target inhibition of several other kinases in the Tec and EGFR families (IC<sub>50</sub> 10 nmol/L and 4.9 nmol/L respectively)<sup>24</sup>. Those off-target interactions are thought to play a role in the unique safety profile of ibrutinib, which, compared with chemoimmunotherapies, includes a higher frequency of rash, diarrhea, arthralgias and myalgias, atrial fibrillation, and major hemorrhage<sup>26</sup>. Next-generation BTK inhibitors have demonstrated improved BTK selectivity, with the highest selectivity reported for acalabrutinib and tirabrutinib, which have the greatest proportion of IC<sub>50</sub> values for off-target kinases (well in excess of 50 nmol/L<sup>24</sup>, Table 1). Whether that greater selectivity will translate into improved safety profiles compared with ibrutinib remains to be seen.



**FIGURE 1** Kinome profiling of Bruton tyrosine kinase (BTK) inhibitors at a single dose of 1  $\mu$ mol/L. Adapted with permission from Figure 1 in Kaptein *et al.*, 2018<sup>24</sup>.

The optimal dosing and frequency for ibrutinib, acalabrutinib, and zanubrutinib were determined in phase I dose-escalation trials based on measurement of BTK occupancy, given that no dose-limiting toxicities were observed<sup>27–29</sup>. The ibrutinib dose of 420 mg once daily was selected because it represented 3 dose levels above the dose achieving 95% or greater BTK occupancy. A twice-daily dose of 100 mg acalabrutinib was selected because it demonstrated BTK occupancy superior to that with 100 mg–400 mg once-daily regimens (median occupancy: 97% when assessed before dose administration on days 8 and 28). For zanubrutinib, the recommended phase II dose of 160 mg twice daily was selected because it demonstrated complete BTK occupancy (>95%) in lymph nodes<sup>29</sup>.

### Reversible Noncovalent Inhibitors

As a consequence of continuous therapy and reliance on the C481 residue for BTK inhibition, patients receiving irreversible BTK inhibitors can develop resistance through mutations of C481, or other mechanisms such as mutations in downstream PLCG2<sup>30</sup>. In one retrospective study of patients from four prospective clinical trials who relapsed on ibrutinib, mutation of C481 was reported in 78% of patients with available samples<sup>31</sup>. The same mechanism of resistance has also recently been reported in patients who relapsed while taking acalabrutinib<sup>32</sup>. To overcome that resistance, a distinct class of reversible BTK inhibitors has emerged that interacts non-covalently with the ATP binding site of BTK<sup>23</sup>. LOXO-305 and ARQ-531 are currently being

**TABLE I** Features of irreversible Bruton tyrosine kinase (BTK) inhibitors with clinical studies in chronic lymphocytic leukemia

Inhibitor	Stage of development	Selectivity	Major off-targets <sup>a</sup>		Recommend dosing	Approvals
			Molecule	Predicted effect of inhibition		
Ibrutinib	III	Low	EGFR ErbB2 ErbB4  Itk Bmx JAK3  Tec Blk Txk	Rash, diarrhea  Infection  Bleeding	420 mg once daily	Health Canada approval in frontline and relapsed settings
Acalabrutinib	III	High	Bmx ErbB4		100 mg twice daily	Health Canada approval in frontline and relapsed setting
Zanubrutinib	II/III	Moderate	Tec Bmx Blk ErbB4 Txk EGFR	Bleeding     Rash, diarrhea	160 mg twice daily	U.S. FDA approval in mantle cell lymphoma
Tirabrutinib	I/II	High	Bmx	—	TBD	

<sup>a</sup> IC<sub>50</sub> < 50 nmol/L, per Kaptein *et al.*, 2018<sup>24</sup>.

EGFR = epidermal growth factor receptor; FDA = Food and Drug Administration; TBD = to be determined.

evaluated in phase I/II clinical trials for B cell malignancies in the relapsed or refractory setting<sup>33,a</sup>; all of which have demonstrated inhibition of BTK in the presence of the C481S mutation *in vitro*<sup>34–36</sup>.

### Efficacy of BTK Inhibitors in Phase III Treatment-Naïve CLL Trials

This section focuses on frontline phase III trials of BTK inhibitors, given their larger sample sizes and ability to compare efficacy against standard treatments available at the time of trial design (Table II).

To date, four phase III trials evaluating ibrutinib in the frontline setting have been conducted. The first of those trials, RESONATE-2, demonstrated a significant improvement in PFS and OS for ibrutinib monotherapy compared with chlorambucil in patients 65 years of age and older [median follow-up: 5 years; 5-year PFS: 70% vs. 12%; hazard ratio (HR): 0.146; 95% confidence interval (CI): 0.098 to 0.218; 5-year OS: 83% vs. 68%; HR: 0.450; 95% CI: 0.266 to 0.761]<sup>39</sup>. Compared with BR, ibrutinib monotherapy also demonstrated a significant PFS benefit in patients 65 years of age and older in the ALLIANCE trial<sup>9</sup>. Additionally, that trial showed a significantly improved PFS for ibrutinib–rituximab compared with BR; however, a PFS benefit for ibrutinib combination therapy over ibrutinib monotherapy was not seen, thus leading to continued use of ibrutinib monotherapy<sup>9</sup>. As with other clinical trials of ibrutinib-based therapy in patients 65 years of age and older with treatment-naïve CLL, the iLLUMINATE trial analysis reported a significant PFS improvement for ibrutinib–obinutuzumab compared

with chlorambucil–obinutuzumab (HR: 0.23; 95% CI: 0.15 to 0.37)<sup>8</sup>. However, with current follow-up, no difference in OS has been observed for ibrutinib-based therapies compared with chemoimmunotherapy in either the iLLUMINATE or the ALLIANCE trial; thus, current practice has not changed across the board nationally<sup>8,9</sup>. The Eastern Cooperative Oncology Group 1912 trial, investigating ibrutinib–rituximab compared with FCR in fit patients up to 70 years of age, found that PFS was significantly improved with ibrutinib-based therapy, which translated into a statistically significant improvement in OS at a median follow-up of 48 months (3-year OS: 99% vs. 93%,  $p = 0.009$ )<sup>7</sup>. Interestingly, in trials comparing ibrutinib-based therapies with chemoimmunotherapy, ibrutinib was associated with a greater benefit in patients with unmutated *IGHV* than in those with mutated *IGHV*, suggesting that, in addition to del(17p), young patients with unmutated *IGHV* might particularly benefit from frontline ibrutinib.

Acalabrutinib has been investigated in a single phase III trial, ELEVATE-TN, in patients 65 years of age and older or with coexisting conditions<sup>10</sup>. The study showed that acalabrutinib monotherapy and acalabrutinib–obinutuzumab both significantly prolonged PFS compared with chlorambucil–obinutuzumab (HR: 0.20; 95% CI: 0.13 to 0.30;  $p < 0.0001$ ; and HR: 0.10; 95% CI: 0.06 to 0.17;  $p < 0.0001$  respectively); however, after a median follow-up of 28.3 months, OS benefit was not detected for either acalabrutinib arm compared with chemoimmunotherapy<sup>10</sup>. Additionally, despite a small trend for improved PFS with acalabrutinib combination therapy compared with monotherapy, the study was not powered to detect a PFS difference between those arms<sup>10</sup>, which will likely result in a preference for acalabrutinib monotherapy over combination therapy because

<sup>a</sup> See NCT03740529 (LOXO-305) and NCT03162536 (ARQ 531) at <https://ClinicalTrials.gov/>.

of ease of administration and a better safety profile. The PFS benefit for the acalabrutinib-containing arms was consistent across subgroups, including in patients stratified by bulky disease, the presence of del(17p), the presence of

del(11q), *IGHV* mutation status (with the exception of the acalabrutinib monotherapy arm), and complex karyotype.

Zanubrutinib continues to be investigated in treatment-naïve CLL in the phase III SEQUOIA (BGB-3111-304)

**TABLE II** Phase III trials of Bruton tyrosine kinase (BTK) inhibitors in treatment-naïve chronic lymphocytic leukemia

Inhibitor and study name	Median follow-up	Population	Treatment arms	PFS	OS
<i>Ibrutinib</i>					
RESONATE-2	29 Months <sup>37</sup>	<i>n</i> =269; del(17p) patients excluded; age: median ~73 years (range: 65–90 years); CIRS>6: ~32%	Ibrutinib vs. chlorambucil (1:1) Crossover to ibrutinib arm allowed upon progression	2-Year <sup>a</sup> : 89% vs. 34% HR <sup>b</sup> : 0.12; 95% CI: 0.07 to 0.20	2-Year: 95% vs. 84% HR <sup>d</sup> : 0.43; 95% CI: 0.21 to 0.86
Alliance A041202	38 Months <sup>9</sup>	<i>n</i> =547; age: median 71 years (range: 65–89 years)	(A) Ibrutinib or (B) ibrutinib–rituximab vs. (C) bendamustine–rituximab (1:1:1) Crossover to ibrutinib monotherapy arm allowed upon progression	2-Year: 88% vs. 87% vs. 74% HR (A vs. C) <sup>b</sup> : 0.39; 95% CI: 0.26 to 0.58 HR (B vs. C) <sup>b</sup> : 0.38; 95% CI: 0.25 to 0.59	2-Year: 90% vs. 94% vs. 95% No difference between groups ( <i>p</i> ≥0.65)
iLLUMINATE	31.3 Months <sup>8</sup>	<i>n</i> =547; age: median ~71 years (range: 66–77 years); CIRS>6: ~32%	Ibrutinib–obinutuzumab vs. chlorambucil–obinutuzumab (1:1) Crossover to ibrutinib monotherapy allowed upon progression	30-Month <sup>c</sup> : 79% vs. 31% HR <sup>b</sup> : 0.23; 95% CI: 0.15 to 0.37	30-Month: 86% vs. 85% HR: 0.92; 95% CI: 0.48 to 1.77
ECOG 1912	48 Months <sup>7</sup>	<i>n</i> =229; del(17p) patients excluded; age: mean 57 years	Ibrutinib–rituximab vs. FCR (2:1) Crossover between arms not allowed	3-Year: 89% vs. 71% HR <sup>b</sup> : 0.39; 95% CI: 0.26 to 0.57	3-Year: 99% vs. 93% HR <sup>e</sup> : 0.34; 95% CI: 0.15 to 0.79
<i>Acalabrutinib</i>					
ELEVATE-TN	28.3 Months <sup>10</sup>	<i>n</i> =535; age: median ~70 years (range: 41–91 years); CIRS-G>6: ~12%	(A) Acalabrutinib or (B) acalabrutinib–obinutuzumab vs. (C) chlorambucil–obinutuzumab (1:1:1) Crossover to acalabrutinib monotherapy arm allowed upon progression	2-Year <sup>c</sup> : 87% vs. 93% vs. 47% HR (A vs. C) <sup>b</sup> : 0.20; 95% CI: 0.13 to 0.30 HR (B vs. C) <sup>b</sup> : 0.10; 95% CI: 0.06 to 0.17	2-Year: 95% vs. 95% vs. 92% HR (A vs. C): 0.60; 95% CI: 0.28 to 1.27 HR (B vs. C): 0.47; 95% CI: 0.21 to 1.06
<i>Zanubrutinib</i>					
SEQUOIA	10 Months <sup>38</sup>	Cohort 1: <i>n</i> ~450 Cohorts 2&3 [del(17p) only]: <i>n</i> ~100 and ~50 Cohort 2 age: median ~70 years (range: 42–86 years)	Cohort 1: zanubrutinib vs. bendamustine–rituximab (1:1) Cohort 2: zanubrutinib monotherapy Cohort 3: zanubrutinib–venetoclax	NA	NA

<sup>a</sup> Investigator-assessed.

<sup>b</sup> *p*<0.001.

<sup>c</sup> Independent review committee–assessed.

<sup>d</sup> *p*=0.0145.

<sup>e</sup> *p*=0.009.

PFS = progression-free survival; OS = overall survival; CIRS = Cumulative Illness Rating Scale; HR = hazard ratio; CI = confidence interval; FCR = fludarabine–cyclophosphamide–rituximab; NA = not available.



trial. That trial is evaluating the efficacy and safety of zanubrutinib compared with BR in patients who are 65 years of age and older or who are unsuitable for treatment with FCR<sup>38</sup>. An additional single-arm cohort is evaluating zanubrutinib in patients with del(17p). At a median follow-up of 10 months, patients with del(17p) receiving zanubrutinib monotherapy showed a best overall response rate of 93%, and only 4 of 109 enrolled patients had progressed on therapy.

### Safety of BTK Inhibitors in CLL and Recommendations for Management

Inhibitors of BTK have a unique safety profile, which includes, relative to chemoimmunotherapy, an increase in rash, diarrhea, arthralgias or myalgias, and cardiovascular and bleeding events. Although the causes of many of those adverse events (AEs) are unclear, they are thought to be associated with inhibition of off-target cellular kinases, an important motivator for the development of next-generation BTK inhibitors. This section summarizes the safety data for ibrutinib, acalabrutinib, and zanubrutinib in the treatment-naïve setting, focusing on AEs of interest and their management (Tables III and IV).

#### Grade 2 or Lower AEs

Diarrhea is thought to be a result of off-target inhibition of the epidermal growth factor receptor (EGFR), given that gastrointestinal toxicities are a well-documented class effect of EGFR inhibitors. In clinical trials of single-agent ibrutinib, rates of all-grade diarrhea are close to 50%<sup>40</sup> (Table III). Diarrhea is generally low-grade (<5% grade 3 or 4) and occurs most frequently within the first 6 months of therapy, with a median duration of 6–20 days<sup>40</sup>.

Rashes associated with BTK inhibitors commonly fall into two categories: a mild non-pruritic petechial rash with later onset (likely related to platelet dysfunction) and an early-onset palpable pruritic rash with variable clinical presentation and severity (possibly related to inhibition of EGFR)<sup>48</sup>. The rash can sometimes be associated with peripheral edema, which can be more difficult to manage. These rashes are generally self-limited (median duration: 31 days) and have been reported to occur in up to 27% of patients receiving ibrutinib within the first year, with the incidence declining over time<sup>26</sup>.

Because acalabrutinib and zanubrutinib have a lower selectivity for EGFR than does ibrutinib, those next-generation BTK inhibitors might lower the incidence of rash and diarrhea; however, head-to-head trials are needed to confirm that hypothesis. In the ELEVATE-TN trial, the incidences of all-grade diarrhea and rash reported for patients with treatment-naïve CLL receiving acalabrutinib monotherapy were 35% and 14% respectively<sup>10</sup>. In the SEQUOIA trial, all-grade diarrhea and rash were each reported in approximately 15% of patients receiving zanubrutinib; however, median follow-up was only 10 months<sup>38</sup>.

Arthralgia is another AE reported to occur more frequently with BTK therapy than with chemotherapy-based regimens<sup>7,8,10</sup>, although the mechanism is unknown. It typically occurs early in treatment and usually resolves within a few months and without therapy modification<sup>40</sup>. In clinical trials, rates of arthralgia reported in patients treated with ibrutinib ranged from 20% to 22%, with most cases being low-grade<sup>8,26</sup>. Thus far, rates of arthralgia reported for acalabrutinib and zanubrutinib in phase III clinical trials appear to be marginally lower than those reported with ibrutinib (Table III).

**TABLE III** Incidence of adverse events (AEs) of interest with Bruton tyrosine kinase inhibitors given as monotherapy in phase III clinical trials for treatment-naïve chronic lymphocytic leukemia

Adverse event	Ibrutinib				Acalabrutinib				Zanubrutinib	
	Monotherapy RESONATE-2 (n=136)		+ Obinutuzumab ILLUMINATE (n=113)		Monotherapy ELEVATE-TN (n=179)		+ Obinutuzumab ELEVATE-TN (n=178)		Monotherapy SEQUOIA (n=109)	
	Median exposure: 28.5 months		Median exposure: 29.3 months		Median exposure: 27.7 months		Median exposure: 27.7 months		Median follow-up: 10 months	
	Grade (%)		Grade (%)		Grade (%)		Grade (%)		Grade (%)	
	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3
Discontinuation for AEs	12	—	16 <sup>a</sup>	—	9	—	11	—	1	—
Diarrhea	45	4	34	3	35	1	39	5	12	1
Arthralgia	20	5	21	1	16	1	22	1	7	0
Headache	—	—	8	0	37	1	40	1	6	1
Atrial fibrillation	10	4	12	5	4	0	3	1	2	1
Hypertension	20	5	17	4	5 <sup>b</sup>	2 <sup>b</sup>	7 <sup>b</sup>	3 <sup>b</sup>	10 <sup>c</sup>	3 <sup>c</sup>
Major bleeding <sup>d</sup>	7	6	—	1	2	2	3	2	4	3
Infection	—	25	—	—	—	14	—	21	—	11

<sup>a</sup> Discontinuation because of any treatment-emergent AE; discontinuation because of a treatment-related AE was 9%.

<sup>b</sup> Hypertension group of preferred terms (standardized MedRA queries).

<sup>c</sup> Hypertension, blood pressure increased, or hypertensive crisis.

<sup>d</sup> Hemorrhage greater than grade 3, serious hemorrhage; or central nervous system hemorrhage of any grade.

**TABLE IV** Suggestions for management of adverse events of interest associated with Bruton tyrosine kinase (BTK) inhibitors in chronic lymphocytic leukemia (CLL)

Adverse event	Management
Diarrhea	<ul style="list-style-type: none"> <li>Typically resolves quickly without need for dose modification<sup>40</sup></li> <li>Antidiarrheals such as loperamide can be used to manage symptoms<sup>40</sup></li> <li>Some situations (for example, fever, abdominal discomfort) should be evaluated for infection<sup>41</sup></li> <li>For grade 3 cases, therapy can be held until reduced to grade 2 or lower, followed by re-initiation of same dose, with option of dose reduction if severe diarrhea recurs<sup>40</sup></li> </ul>
Rash	<ul style="list-style-type: none"> <li>No dose modifications needed, can recover spontaneously without specific treatment<sup>40,42</sup></li> <li>Palpable, pruritic rash may require topical corticosteroids and oral antihistamines<sup>40,42</sup></li> </ul>
Arthralgia	<ul style="list-style-type: none"> <li>Generally, no dose modification needed<sup>40</sup></li> <li>Acetaminophen or short pulses of prednisone can be given<sup>40</sup></li> <li>Anti-inflammatories (for example, ibuprofen) may be used with caution (because of bleeding risk) if not resolved after 6 months<sup>40</sup></li> <li>If persistent and significantly affecting quality of life, dose can be delayed for up to 1 week and reduced upon re-initiating BTK inhibitor<sup>40</sup></li> </ul>
Headache (acalabrutinib)	<ul style="list-style-type: none"> <li>Managed with acetaminophen or caffeine, or both, without the need for dose alteration<sup>40,41</sup></li> </ul>
Atrial fibrillation	<ul style="list-style-type: none"> <li>Inquire about symptoms of arrhythmias and have a low threshold for cardiac workup<sup>43</sup></li> <li>Delaying ibrutinib dose is not recommended in the event of atrial fibrillation because it does not affect the resolution rate<sup>44</sup></li> <li>Management should involve consultation with a cardiologist and assessment of stroke (CHA<sub>2</sub>DS<sub>2</sub>-VASc score) and bleeding (HAS-BLED score) risk<sup>40</sup> <ul style="list-style-type: none"> <li>CHA<sub>2</sub>DS<sub>2</sub>-VASc score 0–1: no anticoagulation required<sup>42</sup></li> <li>CHA<sub>2</sub>DS<sub>2</sub>-VASc score &gt; 2: anticoagulation needed, consider alternative CLL treatment or anticoagulation with newer agent (for example, apixaban, enoxaparin) if HAS-BLED score is low<sup>40–42</sup></li> </ul> </li> <li>Rate or rhythm control (or both) should be achieved, with preference for beta-blockers (diltiazem, verapamil, and amiodarone are inhibitors of CYP3A4 and might increase ibrutinib toxicity; serum amiodarone might increase because of inhibition of P-glycoprotein by ibrutinib)<sup>40</sup></li> <li>Discontinue therapy if unprovoked initial atrial fibrillation occurs within first 3 months of treatment or is recurrent at any point<sup>40</sup></li> </ul>
Ventricular tachycardia (ibrutinib)	<ul style="list-style-type: none"> <li>Discontinue therapy if unprovoked significant ventricular tachycardia occurs within first 3 months or is recurrent at any point<sup>40</sup></li> <li>Inquire about symptoms of arrhythmias and have a low threshold for cardiac work-up<sup>43</sup></li> </ul>
Hypertension	<ul style="list-style-type: none"> <li>Monitor blood pressure regularly<sup>45</sup></li> <li>Upon diagnosis, start antihypertensive therapy without modifying BTK inhibitor dose<sup>40</sup></li> </ul>
Major bleeding	<p><b>Prevention</b></p> <ul style="list-style-type: none"> <li>Concurrent warfarin not recommended; vitamin K antagonist, DOAC, and anti-platelet therapy should be avoided<sup>41</sup></li> <li>If anticoagulation required, alternative CLL therapy or use of a newer anticoagulant (for example, apixaban, enoxaparin) might be practical<sup>41,45</sup></li> <li>Hold BTK therapy 3–4 days before and after minor surgery, or 1 week after major surgery<sup>41</sup></li> </ul> <p><b>Management</b></p> <ul style="list-style-type: none"> <li>Upon major bleeding event, discontinue BTK inhibitor treatment and transfuse with platelets until bleeding is resolved<sup>45</sup></li> </ul>
Infection	<p><b>Prevention</b></p> <ul style="list-style-type: none"> <li>Consider prophylactic acyclovir or valacyclovir because of increased risk of varicella zoster<sup>45</sup></li> <li>Prophylaxis against <i>Pneumocystis jirovecii</i> pneumonia could be considered; however, evidence is weak and further study is needed<sup>46</sup></li> <li>Live-attenuated virus vaccine should be avoided<sup>47</sup></li> </ul> <p><b>Management</b></p> <ul style="list-style-type: none"> <li>Discontinuation not required for grades 1–3 infections<sup>45</sup></li> <li>With grade 4 infection, delay BTK inhibitor dose until resolved to grade 3 or less<sup>45</sup></li> <li>Thoroughly evaluate suspected fungal infections, with high suspicion for aspergillosis<sup>45</sup></li> <li>Evaluate potential drug interactions between BTK inhibitors and anti-infective agents<sup>45</sup></li> <li>If strong CYP3A4 inhibitors are required, reduced BTK inhibitor dose and careful monitoring for toxicity is recommended<sup>45</sup></li> </ul>

CHA<sub>2</sub>DS<sub>2</sub>-VASc = congestive heart failure, hypertension, age, diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism, vascular disease, age, and sex category; HAS-BLED = hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, and drugs or alcohol; DOAC = directly acting oral anticoagulants.

Headache is a frequent low-grade AE specific to treatment with acalabrutinib, the cause being unknown. It occurs in approximately 40% of patients treated with acalabrutinib in clinical trials, is self-limited, and can easily be managed with acetaminophen<sup>10</sup> (Table IV).

### Cardiovascular Events

Atrial fibrillation (AF) is an AE of particular concern with BTK inhibitors, given that its management often includes anticoagulants, which can exacerbate the impaired hemostasis caused by the BTK inhibitors. In first-line trials, AF has been reported in up to 10%–12% of patients with CLL receiving ibrutinib; higher rates have been reported in real-world studies<sup>8,37,49,50</sup>. Atrial fibrillation typically occurs early in ibrutinib treatment, with the rate remaining constant or declining over the course of therapy<sup>39</sup>. For acalabrutinib and zanubrutinib, rates of AF reported thus far in treatment-naïve patients are 4% and 2% respectively, with a minimal proportion of grade 3 or greater cases<sup>10,38</sup> (Table III).

Although the mechanism of ibrutinib-induced AF is unclear, the off-target inhibition of PI3K in cardiac cells is a proposed model, with several *in vitro* and animal studies demonstrating the role of PI3K inhibition in cardiac arrhythmogenesis<sup>51–53</sup>. In one small prospective study, pre-existing cardiac comorbidities and higher left atrial diameter and area were found to increase the risk of AF with ibrutinib<sup>54</sup>. Scoring systems have been developed to predict the risk of incident AF in patients with CLL, one such being the Shanafelt predictive model, which is based on AF risk factors (older age, male sex, valvular heart disease, and hypertension) identified from a retrospective study<sup>55</sup>.

Ventricular arrhythmias and sudden deaths are rare AEs that have thus far been reported only in patients treated with ibrutinib-based therapies (10 cases in 1000 patients in clinical trials, 13 cases in the U.S. Food and Drug Administration's Adverse Event Reporting System)<sup>43</sup>, with no current evidence in the published literature showing that such events occur with next-generation BTK inhibitors. Several case reports have identified ventricular arrhythmias in ibrutinib-treated patients with a history of AF and cardiomyopathy<sup>56,57</sup>. In a retrospective analysis of 582 patients receiving ibrutinib, multivariable analysis found prior AF to be the only factor associated with development of ventricular or supraventricular arrhythmic events<sup>58</sup>.

Hypertension is frequently observed in patients receiving ibrutinib-based therapy, occurring in up to 20% of patients in clinical trials<sup>37</sup> and more frequently in real-world studies (ranging from 35% to 78%, with varying diagnostic criteria)<sup>59,60</sup>. In a retrospective study of 562 patients with B cell malignancies who received ibrutinib-based therapy, the development of new or worsened hypertension was associated with a risk of other cardiac events that was increased by a factor of 2; however, initiation of antihypertensive agents was associated with a lower risk of major cardiovascular events<sup>60</sup>. That finding, together with the observation that the prevalence of hypertension increases over the course of ibrutinib treatment<sup>26</sup>, highlights the importance of proper monitoring and management of this AE (Table IV).

The mechanism of hypertension associated with ibrutinib has not been elucidated; however, indirect down-regulation of PI3K–p110 $\alpha$  or of vascular endothelial growth

factor has been postulated to contribute<sup>60</sup>. Thus far, rates of any-grade hypertension reported in phase III clinical trials of acalabrutinib and zanubrutinib in treatment-naïve CLL (5% and 10% respectively, Table III) are lower than the rates observed with ibrutinib<sup>10,38</sup>. However, it will be important to confirm those observations with long-term follow-up and real-world data.

### Bleeding

In clinical trials, minor bleeding and bruising are frequently reported in patients receiving ibrutinib (up to 50%)<sup>26</sup>; major events occur in up to 11% with long-term follow-up<sup>39</sup>. Bleeding of any grade most commonly occurs within the first year of therapy, but can occur at a substantial rate throughout the course of ibrutinib therapy<sup>26</sup>. In analyses of the RESONATE-2 and ELEVATE-TN trials, with a similar median follow-up, the rates of grade 3 or greater hemorrhage with ibrutinib and acalabrutinib monotherapy were 6% and 2% respectively<sup>10,37</sup> (Table IV). The rate of grade 3 or greater hemorrhage with zanubrutinib in the phase III SEQUOIA trial is 3%; however, median follow-up is only 10 months<sup>38</sup>.

Real-world studies of ibrutinib report a higher frequency of grade 3 or greater hemorrhage, with one retrospective analysis reporting a rate of 19%<sup>61</sup>. Of the affected patients, 74% were taking concomitant anticoagulation or antiplatelet therapy (or both), which has been found to be a significant risk factor for major hemorrhage<sup>61</sup>. Head-to-head trials controlling for anticoagulant or antiplatelet therapy will therefore be needed to determine a difference in the risk of bleeding between ibrutinib and the next-generation inhibitors.

Several mechanisms potentially explain an increase in bleeding events with ibrutinib and other BTK inhibitors compared with chemotherapy-based regimens. First, the BTK inhibitors inhibit both BTK and Tec, which are involved in promoting platelet aggregation downstream of glycoprotein VI<sup>62,63</sup>. Second, inhibition of Src family kinases has been found to cause hemostatic dysfunction that is linked to increased risk of bleeding<sup>64</sup>. The lower selectivity for ibrutinib compared with acalabrutinib and zanubrutinib, particularly with respect to Tec inhibition, could potentially explain the decrease in bleeding events observed with next-generation inhibitors. Indeed, *in vitro* studies have noted dysfunctional thrombus formation under arterial flow with ibrutinib treatment that does not appear to occur with acalabrutinib and zanubrutinib<sup>65,66</sup>.

### Infection

Clinical trials investigating ibrutinib in patients with B cell malignancies have revealed an increased rate of infection, particularly with pneumonia caused by opportunistic pathogens<sup>67</sup>. The high frequency of infection is likely attributable, at least in part, to a combination of ibrutinib-mediated inhibition of BTK and Itk (expressed in T cells), which together alter innate and adaptive immune function<sup>67</sup>. In the RESONATE-2 trial, the incidence of grade 3 or greater infections in patients with treatment-naïve CLL was 25% at a median follow-up of 28.5 months, with an incidence of 12% for pneumonia in the 5-year analysis<sup>37,39</sup>. Infections most frequently occur early in treatment; however, some events can occur with prolonged use<sup>26</sup>.

Infections also occur with next-generation BTK treatment, although possibly to a lesser extent because of less Itk inhibition. In ELEVATE-TN, grade 3 or greater infections occurred at a rate of 14% in the acalabrutinib monotherapy arm (Table III), with 3% of patients acquiring pneumonia<sup>10</sup>. At a median follow-up of 10 months, the rate of grade 3 or greater infections observed in patients treated with zanubrutinib in the SEQUOIA trial was 11%<sup>38</sup>.

Infections of particular concern in ibrutinib-treated patients include the fungal infections *Aspergillus fumigatus* (reported to occur at a rate of 2% in a large retrospective study of patients with lymphoid malignancy<sup>68</sup>) and *Pneumocystis jirovecii* pneumonia (estimated to occur at a rate of 2 cases per 100 patient-years in a single-institution retrospective study<sup>69</sup>). Concomitant use of steroids has been associated with an increased risk for those invasive fungal infections<sup>70</sup>. The management of fungal infections remains challenging, because many of the optimal treatments are strong CYP3A4 inhibitors, which can increase the serum concentration of BTK inhibitors; however, that effect can be managed with dose reductions<sup>40</sup> (Table IV).

### Discontinuations Related to AEs

The current standard of care is to administer BTK inhibitors continuously until disease progression, suggesting that long-term drug tolerability could be important to achieving optimal outcomes. However, poor tolerability has so far been managed with dose reductions or interruptions<sup>50,71,72</sup>, and recent data from the Eastern Cooperative Oncology Group 1912 study demonstrated that patients who discontinued ibrutinib for reasons other than progression or death had a median PFS of 22.5 months post-discontinuation<sup>7</sup>. In frontline phase III trials of ibrutinib and acalabrutinib, rates of treatment discontinuation because of AEs were similar after a median follow-up of approximately 30 months, being reported in approximately 10% of enrolled patients<sup>8,10,37</sup> (Table III). Those discontinuation rates are comparable to the rates reported in phase III trials in the relapsed setting<sup>73,74</sup>. The AEs most commonly leading to ibrutinib discontinuation in the RESONATE-2 and ILLUMINATE trials were infection, hemorrhage, AF, rash, and thrombocytopenia<sup>8,37</sup>. The ELEVATE-TN trial reported 16 discontinuations, with 1 discontinuation for each AE, such as myocardial infarction, brain injury, and brain neoplasm, among others<sup>10</sup>. With early follow-up in the SEQUOIA trial, 1 patient (1%) discontinued zanubrutinib because of pneumonia, which led to death<sup>38</sup>.

The rate of ibrutinib discontinuation for AEs is higher in real-world studies than in clinical trials, with one U.S. study of 616 patients receiving ibrutinib in the frontline or relapsed setting showing a rate of 20%<sup>50</sup>. In that study, AF was a frequent cause of ibrutinib discontinuation, accounting for 25% and 12% of AE-related discontinuations in patients with treatment-naïve and relapsed disease respectively. Adverse events such as arthralgia (41.6%) and rash (16.7%) were among the most frequent AEs leading to discontinuation in the treatment-naïve setting, and diarrhea accounted for 6.6% of AE-related discontinuations in the relapsed setting. Infection (10.7%), pneumonitis (9.9%), and bleeding (9%) were also frequent reasons for discontinuation in the relapsed setting.

### Canadian Perspective

Therapy with BTK inhibitors continues to be an effective strategy for treating patients with CLL in the frontline setting, particularly in high-risk disease. In the absence of head-to-head trials, it is reassuring that, in cross-trial comparisons (phase III studies), ibrutinib and acalabrutinib appear to have comparable efficacy in treatment-naïve patients more than 65 years of age, with the 2-year PFS for ibrutinib or acalabrutinib monotherapy ranging between 87% and 89%<sup>9,10,37</sup>. In the ILLUMINATE and ELEVATE-TN trials, combination ibrutinib–obinutuzumab and acalabrutinib monotherapy, compared with chlorambucil–obinutuzumab, were both associated with similar reductions in the relative risk of progression or death (77% and 80% respectively), while acalabrutinib–obinutuzumab was associated with the numerically highest reduction in relative risk (90%). However, potential differences in the performance of the chlorambucil–obinutuzumab arm in the ILLUMINATE (median PFS: 19 months; 95% CI: 15.1 months to 22.1 months) and ELEVATE-TN trials (median PFS: 22.6 months; 95% CI: 20.2 months to 27.6 months) and differences in baseline patient characteristics pose a challenge in interpreting the results<sup>8,10</sup>.

In terms of safety, ibrutinib, acalabrutinib, and zanubrutinib are generally tolerable, albeit with somewhat different toxicity profiles, likely related to differences in off-target effects. Headache is certainly more frequent with acalabrutinib therapy, although the mechanism for the difference is unclear. Based on current data, cardiovascular toxicities, including hypertension and AF, appear to be less frequent with the newer BTK inhibitors than with ibrutinib. Ventricular tachycardia and sudden death have not been observed with the former agents. Because some cardiovascular events will occur after prolonged exposure to ibrutinib and because the incidences of those events are higher in clinical practice, longer follow-up and real-world data for the next-generation BTK inhibitors will be needed to better assess the true risk of cardiovascular events. The need for longer experience also applies to bleeding, infection, and arthralgia, which might occur at lower frequencies with the next-generation inhibitors. Head-to-head trials will confirm whether next-generation BTK inhibitors have an improved safety profile compared with that for ibrutinib. Two upcoming head-to-head phase III trials in relapsed or refractory CLL, which will compare ibrutinib with either acalabrutinib [ELEVATE-RR, primary endpoint PFS (see NCT02477696 at <https://ClinicalTrials.gov/>)] or zanubrutinib [ALPINE, primary endpoint overall response (NCT03734016)] will provide clarity about the difference in safety between first-in-class and newer BTK-targeted agents.

In the absence of comparative efficacy and safety data, a number of factors should be considered when deciding on frontline therapy for CLL. For patients with known heart failure, low ejection fraction, or premature ventricular contractions, acalabrutinib might be preferred to ibrutinib because of its lower cardiac toxicity profile and lack of an association with ventricular arrhythmias and sudden death. In addition, in patients with skin toxicities, acalabrutinib might be preferable to ibrutinib because its increased specificity reduces EGFR-mediated toxicities. The highly



selective BTK inhibitor zanubrutinib is being studied as a novel alternative, along with other novel BTK inhibitors currently in development.

Obviously, drug availability plays a significant role in therapy selection, which is limited first by Health Canada approval and second by reimbursement, which is variable across provinces. Given that reimbursement criteria are often dictated by a patient's CLL genetics and *IGHV* mutational status, access to molecular testing is critical for drug access—a factor that also varies by province and institution. Treatment selection might also be influenced by the availability of health care resources. Regimens containing chemoimmunotherapy are currently given intravenously, which is limited by access to chair time for the infusion. Initiation of venetoclax–obinutuzumab (dose ramp-up), another first-line option, is also resource-intensive because, in addition to the intravenous infusion of obinutuzumab, it often requires patients to be admitted to hospital at the beginning of treatment to monitor for tumour lysis syndrome. Oral agents might be more costly because of the indefinite nature of therapy; however, the reduced strain on hospital resources could be an important factor at some centres and can be helpful in situations such as the current COVID-19 pandemic, in which such resources are limited.

In a situation in which many effective treatments are accessible in the first-line setting, clinicians should inform patients about the risks and benefits of all treatment options, taking into consideration their age, comorbidities, concomitant medications, and disease features. Patient preference could play a significant role in therapy selection, particularly in older patients for whom BTK therapy, compared with chemoimmunotherapy, has not yet demonstrated an OS benefit. Some patients might prefer to receive a time-limited treatment (chemotherapy or venetoclax–obinutuzumab, if available) rather than continuous BTK therapy; others might prefer oral agents if attending a centre for infusion is challenging because of travel time, mobility issues, or reliance on caregivers. If a patient prefers to receive a BTK inhibitor as first-line treatment, a discussion of safety profiles, dosing schedules, and clinician experience might dictate the choice of BTK inhibitor.

## SUMMARY

Over the next decade, the frontline treatment landscape in CLL might shift to fixed-duration combinations of novel agents with variable treatment durations and potential for minimal residual disease–guided therapy, given that several clinical trials are now investigating regimens that combine Bcl-2 and BTK inhibitors<sup>75,76</sup>. While the data from those trials mature, long-term follow-up data from current phase III trials could clarify whether BTK inhibitor therapy will show a survival advantage over chemoimmunotherapy in younger and older patients with CLL, and whether patients with both unmutated and mutated *IGHV* status will benefit from the novel agents. Additional studies investigating noncovalent BTK inhibitors and the efficacy of BTK inhibitors after frontline therapy with venetoclax will provide further information on which to base treatment decisions in the future. Because patients with CLL are

heterogeneous in their disease biology, age, general health, and lifestyle, it will be important to continue to have many therapeutic options so as to optimally treat their disease and support quality of life.

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