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Review Article

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Managing Ibrutinib-Intolerant Patients With B-Cell Malignancies

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Abstract

Ibrutinib is a first-generation inhibitor of Bruton tyrosine kinase (BTK) that is currently approved to treat patients with B-cell malignancies, including Waldenström macroglobulinemia (WM), relapsed/refractory (R/R) mantle cell lymphoma (MCL), R/R marginal zone lymphoma (MZL), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Off-target adverse effects, such as atrial fibrillation, hypertension, and bleeding, have been observed and may limit a patient's tolerance for treatment. Currently, there is no well-established treatment regimen for patients who cannot tolerate ibrutinib. Approaches to address such patients include managing ibrutinib side effects with supportive care or dose reductions, switching to an alternative covalent BTK inhibitor, or abandoning covalent BTK inhibitors for alternative forms of treatment. Here we review the literature and provide guidance on treating ibrutinib-intolerant patients with B-cell malignancies.

Key words: Waldenström macroglobulinemia; chronic lymphocytic leukemia; marginal zone lymphoma; mantle cell lymphoma; Bruton's tyrosine kinase.

Implications for Practice

Bruton tyrosine kinase (BTK) inhibition has been demonstrated to be a highly effective treatment strategy in patients with B-cell malignancies. Ibrutinib, a first-generation BTK inhibitor, has become a cornerstone treatment; however, up to half of the patients treated with ibrutinib experience off-target effects including atrial fibrillation, hypertension, and bleeding, among other adverse events. There is currently no well-established treatment algorithm for patients with B-cell malignancies who experience ibrutinib intolerance. Herein we describe our approach to treating ibrutinib-intolerant patients with B-cell malignancies.

Introduction

Ibrutinib is a first-generation inhibitor of Bruton tyrosine kinase (BTK), which is a key intracellular mediator of B-cell receptor signaling that promotes the growth and survival of malignant B cells.[1,2] Currently, ibrutinib is approved by the US Food and Drug Administration (FDA) to treat multiple types of non-Hodgkin B-cell malignancies, including Waldenström macroglobulinemia (WM), previously treated mantle cell lymphoma (MCL), marginal zone lymphoma (MZL) previously treated with at least 1 prior anti-CD20-based therapy, and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; including patients with 17p deletion).[3] WM is a rare, incurable, non-Hodgkin B-cell lymphoma caused by the malignant accumulation of lymphoplasmacytic lymphoma cells in the bone marrow and other organs secreting a monoclonal IgM paraprotein.[4,5] Approximately 3-4 cases of WM are reported annually per million people in the US and Europe, and it is more common in White males over 60 years of age.[5-7] MCL is a form of non-Hodgkin B-cell lymphoma that arises from a malignant transformation of B lymphocytes in the mantle zone of lymph node follicles.[8,9] Its annual incidence is 1 case per 200 000 people, and it is more common in men than in women (3:1), with a median age at diagnosis ranging from 60 to 70 years.[10] MZL is a group of indolent B-cell non-Hodgkin lymphomas that make up 5%-15% of non-Hodgkin lymphoma cases in the Western world.[11] The median age of diagnosis for MZL is 67 years and the overall age-adjusted incidence rate is 19.6 per 1 000 000 person-years.[12,13] CLL/SLL are considered 2 manifestations of the same disease and are characterized by progressive accumulation of leukemic cells in the peripheral blood, bone marrow, and lymphoid tissue.[14] The age-adjusted incidence of CLL/SLL in the US is 4.1/100 000 persons, and the median age of diagnosis is 72 years. More males than females are affected by CLL, with a 1.7:1 male-to-female ratio.[15]

Current treatment guidelines highlight the use of several treatment options for the B-cell malignancies described above, including the Bruton tyrosine kinase (BTK) inhibitors ibrutinib (±rituximab), acalabrutinib, and zanubrutinib.[16-19] Clinical trial data have shown that treatment with ibrutinib produced good responses in patients with WM (monotherapy: 2-year progression-free survival [PFS], 69.1%[20]; 4-year

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PFS, 76%[21]; 5-year PFS, 38%-70%[22]; in combination with rituximab: 30-month PFS, 82%[23]; 54-month PFS, 63%-72%[24]), MCL (overall response rate [ORR], 68%; median duration of response [DOR], 17.5 months[25]), MZL (ORR, 48%[26]), and CLL/SLL (relapsed/refractory [R/R] CLL/SLL ORR, 91%[27]; treatment naïve [TN] CLL/SLL ORR, 92%[28]; in combination with bendamustine + rituximab ORR, 87.2%[29]). Thus, ibrutinib has become a cornerstone treatment for these patients.

Despite its efficacy, ibrutinib has well-described off-target effects including atrial fibrillation (5%-12%), hypertension (5%-13%), and bleeding (51% of patients treated with ibrutinib + rituximab) that may warrant dose reductions or treatment discontinuations.[20,23] In a real-world study investigating dose reductions or discontinuations in patients with CLL, 22.8% of patients experienced a dose reduction and 20.6% discontinued ibrutinib due to an adverse event (AE).[30] In this study, the most common AEs leading to discontinuation of ibrutinib were atrial fibrillation (24% of patients who discontinued ibrutinib), gastrointestinal disorders (24%), infections/infestations (19%), hematologic abnormalities (16%), and fatigue (14%). In another real-world study of ibrutinib in patients with CLL, 91/209 (43.5%) patients had a temporary dose interruption, and after a median of 20 months on therapy, 37/209 (17.7%) patients discontinued therapy due to a toxicity, including infection (21.6%), cardiovascular event (13.5%), hematologic toxicity (13.5%), bleeding (10.8%), atrial fibrillation (8.1%), diarrhea (8.1%), musculoskeletal pain (5.4%), or other (18.9%).[31] In a real-world study of patients with WM treated with ibrutinib, 95/385 (25%) patients required at least 1 dose reduction, and the most common reasons for dose reduction were rheumatologic AEs (myalgias, arthralgias, or muscle cramping; 28.4%), cardiac AEs (arrhythmia, hypertension, or palpitations; 17.9%), cytopenias (16.8%), nail/skin/hair changes (14.7%), gastrointestinal symptoms (diarrhea, nausea, or reflux; 11.6%), and bleeding/bruising (10.5%).[32] In addition, ibrutinib has drug–drug interactions with CYP3A inhibitors and CYP3A inducers, so patients who require comedication with such agents are limited in their use of ibrutinib.[3,33] Furthermore, patients with WM who discontinue ibrutinib treatment require close monitoring and are at risk for rapid rebounds in serum IgM and symptomatic hyperviscosity within weeks of stopping therapy.[34] As there is no well-established treatment algorithm for how to manage patients who experience ibrutinib intolerance, herein we describe our approach to managing ibrutinib intolerance in patients with B-cell malignancies.

Approaches to Address Ibrutinib Intolerance

The overall goal of therapy for patients with B-cell malignancies is to balance a durable response while improving individual quality of life. Guidelines for the treatment of WM, MCL, MZL, and CLL/SLL published by the National Comprehensive Cancer Network (NCCN) provide a wealth of information for efficacious treatment options.[17-19] In addition to ibrutinib, recommended first-line regimens for CLL include acalabrutinib ± obinutuzumab, venetoclax + obinutuzumab, and zanubrutinib.[17] For WM they include bendamustine/rituximab, bortezomib/dexamethasone/rituximab, and zanubrutinib.[18] For both MCL and MZL, ibrutinib is recommended for second-line and subsequent therapy, along with acalabrutinib, zanubrutinib, and lenalidomide + rituximab.[19] However, the optimal treatment for patients experiencing ibrutinib intolerance has yet to be established and the application of a personalized approach is warranted. Three logical treatment strategies address ibrutinib intolerance (Fig. 1): (1) manage ibrutinib side effects via supportive care or dose reductions; (2) switch patients to another covalent BTK inhibitor; or (3) abandon covalent BTK inhibitors for an alternate treatment option. For each treatment strategy, we looked to data from studies of patients with prior treatment with BTK inhibitors for guidance.

Strategy 1: Manage Side Effects

In many patients, ibrutinib tolerability can be improved by reducing the dosage, or by individualized management of relevant side effects. Table 1 summarizes various strategies to manage side effects of ibrutinib to improve its tolerability. While managing side effects by prescribing additional medications may be optimal for some patients, evidence from patients with WM suggest that a dosage reduction alone may resolve ibrutinib intolerance in some while maintaining the hematologic response.[32]

The approved dosage of ibrutinib for patients with MCL and MZL is 560 mg once daily (QD) and for patients with CLL/SLL and WM is 420 mg QD.[3] However, higher dosages were shown to be equally effective with less tolerability.[44,45] In a retrospective analysis of 385 patients with WM who received ibrutinib, 95 patients (25%) required a dosage reduction. The most common reasons for dosage reductions (incidence ≥ 10 patients) were events related to musculoskeletal symptoms (n = 27), cardiac symptoms (n = 17), cytopenias (n = 16), nail/skin/hair changes (n = 14), gastrointestinal symptoms (n = 11), and bleeding/bruising (n = 10). Nearly two-thirds of patients who had a dosage reduction experienced improvements in or resolution of their AEs (improvements in at least 1 AE: 40 patients [42%]; complete resolution: 22 patients [23%]). Twenty-six patients (27%) experienced no change in AEs and 10 of these patients required an additional dosage reduction; following the second dosage reduction, 5 patients had improvement or resolution of symptoms. Of the 48 patients with dosage reductions and 1-year hematologic follow-up data, 10 patients (21%) had improvement in hematologic response, 35 patients (73%) maintained their response, and 3 (6%) had worsening of their response.

Another study investigated the impact of reducing ibrutinib dose in patients with CLL at Mayo Clinic from 2013 to 2017.[31] In this retrospective study, 48/122 patients who started at the standard dose of 420 mg daily experienced a dose modification at least once. The most common reasons for

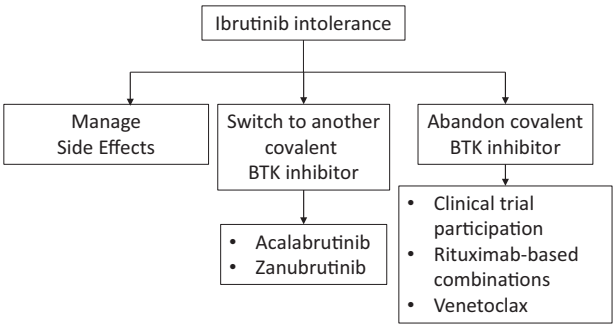

Figure 1. Suggested treatment algorithm in patients intolerant of ibrutinib. Abbreviation: BTK, Bruton tyrosine kinase.

Table 1. Potential management strategies for common side effects of ibrutinib.

Side effect	Proposed management strategy
Atrial fibrillation[35–37]	• Consult with cardiologist and estimate risk of stroke (ie, with CHA_2DS_2-VASc risk stratification tool) • Rate and rhythm control agents such as digoxin, bisoprolol, or amiodarone can be administered • Anticoagulation/antiplatelet agents such as direct oral anticoagulants can be administered, although there is an increased risk of bleeding • Beta blockers • Electrical cardioversion such as a pacemaker • Reduce ibrutinib dose • Consider an alternative BTK inhibitor
Bleeding/bruising[36,38]	• Bleeding events may decrease after 6 months with ibrutinib • Remove or reduce the dose of concomitant anticoagulants if possible • Council patients to avoid aspirin, non-steroidal anti-inflammatory drugs, vitamin E, and fish oils, if possible • Reduce ibrutinib dose
Diarrhea[39,40]	• Typically resolves on its own • Dose holds and dose reductions can be effective • Antidiarrheal treatments such as loperamide, diphenoxylate/atropine, bismuth subsalicylate, or probiotics
Musculoskeletal pain/arthralgia[37]	• Can resolve on its own over time • Treat pain with acetaminophen or prednisone (avoid ibuprofen) as needed • Consider referral to rheumatology for persistent pain • Hold ibrutinib (up to 7 days) and then restart with reduced dose
Rash[41]	• Topical corticosteroid therapy to treat minor rash • Oral antihistamines can treat severe rash • Ibrutinib dose interruption or dose reduction may be necessary
Infection[37]	• Treat with appropriate anti-infective agents, with careful attention to drug interactions (ie, CYP3A4 inhibitors) • If strong inhibitors of CYP3A4 are needed, reduce dose of ibrutinib and monitor for toxicity
Hypertension[37]	• Monitor blood pressure and medically manage hypertension along with primary care physician • Monitor for atrial fibrillation
Anemia/neutropenia/thrombocytopenia[3,42]	• Dose reduction • Consider use of growth factors as needed for neutropenia
Fatigue[43]	• Dose hold or dose reduction

Abbreviations: BTK, Bruton tyrosine kinase; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65-74 and sex category (female); CYP3A4, cytochrome P450 3A4.

dose modification were hematologic toxicity (n = 16), atrial fibrillation (n = 10), drug–drug interaction (n = 9), musculoskeletal pain (n = 6), rash (n = 6), bleeding (n = 5), diarrhea (n = 5), and physician/patient preference (n = 5). In addition, 91 of the total 209 patients with CLL experienced a dose interruption during ibrutinib therapy (common reasons included hematologic toxicity, atrial fibrillation, bleeding, diarrhea, infection, musculoskeletal pain, rash, and procedures). The study found that temporary dose interruption was associated with a shorter event free survival (EFS) in these patients, although EFS and overall survival (OS) were not affected by reduction from the standard dose. After a median time of 20 months on ibrutinib therapy, 61/209 patients discontinued therapy, 37 of which were due to toxicities.

These safety data suggest that ibrutinib dosage reduction is a viable option to address ibrutinib intolerance without compromising hematologic response in some patients. Further research is required to identify which patients may benefit from an ibrutinib dosage reduction rather than switching.

Strategy 2: Switch Patients to Another Covalent BTK Inhibitor

For patients with disease that is not resistant to BTK inhibitor therapy and with persistent adverse effects despite the above-mentioned strategies, an additional option for managing ibrutinib intolerance may be to switch to another covalent BTK inhibitor. Ongoing studies are actively exploring the use of acalabrutinib and zanubrutinib in ibrutinib-intolerant patients with B-cell malignancies, and the findings from these studies are highly anticipated (Table 2).

Acalabrutinib Vs. Ibrutinib

While acalabrutinib does not yet have FDA approval for WM or MZL (at the time of this writing), it is approved for CLL/SLL and MCL.[46] A head-to-head comparison of acalabrutinib vs. ibrutinib in CLL has also been conducted (NCT02477696).[47] This study compared the effects of acalabrutinib vs. ibrutinib in 533 patients with R/R CLL and found that acalabrutinib was noninferior to ibrutinib, with a median PFS of 38.4 months in both arms. In addition, rates of atrial fibrillation/flutter were significantly lower in patients treated with acalabrutinib vs. ibrutinib (9.4% vs. 16.0%, P = .02). Discontinuation due to AEs was also lower in the acalabrutinib arm vs. the ibrutinib arm (14.7% vs. 21.3%).

Although direct comparative studies of acalabrutinib and ibrutinib are not yet available in WM and MZL, ongoing studies are investigating the use of acalabrutinib in these diseases. A phase II, single-arm, open-label study (NCT02180724)

Table 2. Selected clinical trials of covalent BTK inhibitor switch studies in ibrutinib-intolerant patients with various B-cell malignancies.

Title	Condition	NCT	URL
A study of ACP-196 (acalabrutinib) in subjects with relapsed/refractory CLL and intolerant of ibrutinib therapy	R/R CLL	NCT02717611	https://clinicaltrials.gov/ct2/show/NCT02717611
Zanubrutinib (BGB-3111) in participants with previously treated B-cell lymphoma intolerant of prior Bruton tyrosine kinase inhibitor treatment	CLL/SLL, MCL, MZL, WM	NCT04116437	https://clinicaltrials.gov/ct2/show/NCT04116437
Acalabrutinib for the treatment of ibrutinib-intolerant mantle cell lymphoma	MCL	NCT04189757	https://clinicaltrials.gov/ct2/show/NCT04189757

Abbreviations: CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NCT, National Clinical Trial; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

evaluating the safety, pharmacokinetics, pharmacodynamics, and activity of acalabrutinib in patients with WM is ongoing.[48] Interim results from 106 patients who received oral acalabrutinib 100 mg twice daily showed that 13 of 14 (93%) patients with treatment-naïve WM and 86 of 92 (93%) patients with R/R WM achieved an overall response; the median follow-up was 27.4 months. Acalabrutinib had a manageable safety profile in patients with WM. Grade 3/4 atrial fibrillation occurred in 1 (1%) patient and grade 3/4 bleeding occurred in 3 (3%) patients. Half of the treatment-naïve and 25% of the R/R patients discontinued treatment. In addition, a phase Ib/II, multicenter, open-label trial of acalabrutinib in patients with R/R MZL is also underway (NCT02180711). Results from 40 evaluable patients with R/R MZL receiving acalabrutinib 100 mg twice daily showed an ORR of 53% (95% CI, 36%-69%), and 5 (13%) patients had complete responses (median follow-up was 13.3 months).[49] In this study, there were 5 deaths (n = 4 disease progression, n = 1 septic shock), and the most common ≥ Grade 3 AEs were neutropenia (14%), anemia (7%), dyspnea (7%), fatigue (5%), and thrombocytopenia (5%). Further studies are needed to compare the efficacy and safety of acalabrutinib to other current standard treatments of B-cell malignancies, and to investigate acalabrutinib in ibrutinib-intolerant patients.

Acalabrutinib in Ibrutinib-Intolerant Patients with CLL

In an open-label, phase II study (NCT02029443), the safety and efficacy of acalabrutinib, a covalent BTK inhibitor with greater selectivity than ibrutinib, at a dosage of 100 mg twice daily or 200 mg once daily was evaluated in patients with CLL who discontinued treatment because of ibrutinib intolerance.[50] The 33 patients treated with acalabrutinib in this study (61% men; median age, 64 years; range, 50-82 years) had received ibrutinib for a median duration of 11.6 months (range, 1-62 months). Patients started acalabrutinib a median time of 47 days (range, 3-331 days) after ibrutinib discontinuation. The most frequently reported AEs with acalabrutinib (incidence ≥ 20%) were diarrhea (58%), headache (39%), cough (33%), weight gain (30%), nausea (27%), contusion (24%), upper respiratory tract infection (24%), arthralgia (21%), pyrexia (21%), and vomiting (21%). The most common grade ≥ 3 AEs (incidence ≥ 2 patients) were neutropenia (n = 4; 12%); thrombocytopenia (n = 3; 9%); and pneumonia, anemia, and hypertension (n = 2 each; 6%). Of 61 ibrutinib-related AEs associated with ibrutinib intolerance, 72% did not recur and 13% recurred at a lower grade with acalabrutinib treatment (Fig. 2). Twenty-one patients (64%) did not experience a recurrence of AEs that led to ibrutinib intolerance. Fatigue, rash, myalgia, and diarrhea were the most common AEs that recurred (incidence > 1 patient).

Another phase II study (NCT02717611) was conducted to investigate acalabrutinib in patients with CLL that were intolerant to ibrutinib as defined by specific criteria: discontinued ibrutinib due to persistent grade 3 or 4 AEs, or persistent/recurrent grade 2 AEs despite dosage reduction or interruption, and despite optimal supportive care.[51] In this study, 60 patients (63% men; median age, 69.5 years; range, 43-88 years) were treated with acalabrutinib 100 mg orally twice daily until disease progression or intolerance. The patients had a median duration of 5.7 months (range <1-55.5 months) of former ibrutinib treatment, and 25% of patients received ibrutinib for <2 months. The median time from stopping treatment with ibrutinib to starting treatment with acalabrutinib was 7.5 months. The most common AEs during acalabrutinib treatment were diarrhea (n = 32, 53%), headache (n = 25, 42%), contusion (n = 24, 40%), dizziness (n = 20, 33%), upper respiratory tract infection (n = 20, 33%), and cough (n = 18, 30%). Ibrutinib-intolerance AEs recurred in 24 of the 60 patients (40%) during acalabrutinib treatment, although 67% of these events were lower grade with acalabrutinib than with ibrutinib treatment, 30% were of an unchanged grade, and 1 event (4%; grade 3 increased liver function test) was of a higher grade. The most common recurring ibrutinib-intolerance events on acalabrutinib treatment were diarrhea (n = 5) and bleeding events (n = 5).

Zanubrutinib Vs. Ibrutinib

Zanubrutinib, a covalent BTK inhibitor with higher selectivity than ibrutinib and acalabrutinib, is currently approved for treating WM, R/R MCL, and R/R MZL in patients who have received at least 1 anti-CD20-based regimen.[52] Several trials have investigated the use of zanubrutinib to treat various B-cell malignancies.[53-57] A pooled analysis of safety from 6 studies investigating zanubrutinib monotherapy in B-cell malignancies found that it was generally well tolerated and had a safety profile that was manageable and mostly reversible.[57] Though zanubrutinib is not currently approved to treat patients with CLL/SLL, the ongoing ALPINE trial (NCT03734016) is a phase III global randomized study that compares the use of zanubrutinib vs. ibrutinib to treat patients with R/R CLL/SLL.[58] Interim results from 415 patients showed that the primary outcome of ORR was significantly higher in patients treated with zanubrutinib vs. ibrutinib (78.3% vs. 62.5%, 2-sided P = .0006), and the rates of atrial fibrillation/flutter (2.5% vs. 10.1%), major bleeding (2.9% vs. 3.9%), and AEs leading to discontinuation (7.8% vs. 13.0%) or death (3.9% vs. 5.8%) were all lower with zanubrutinib vs ibrutinib.

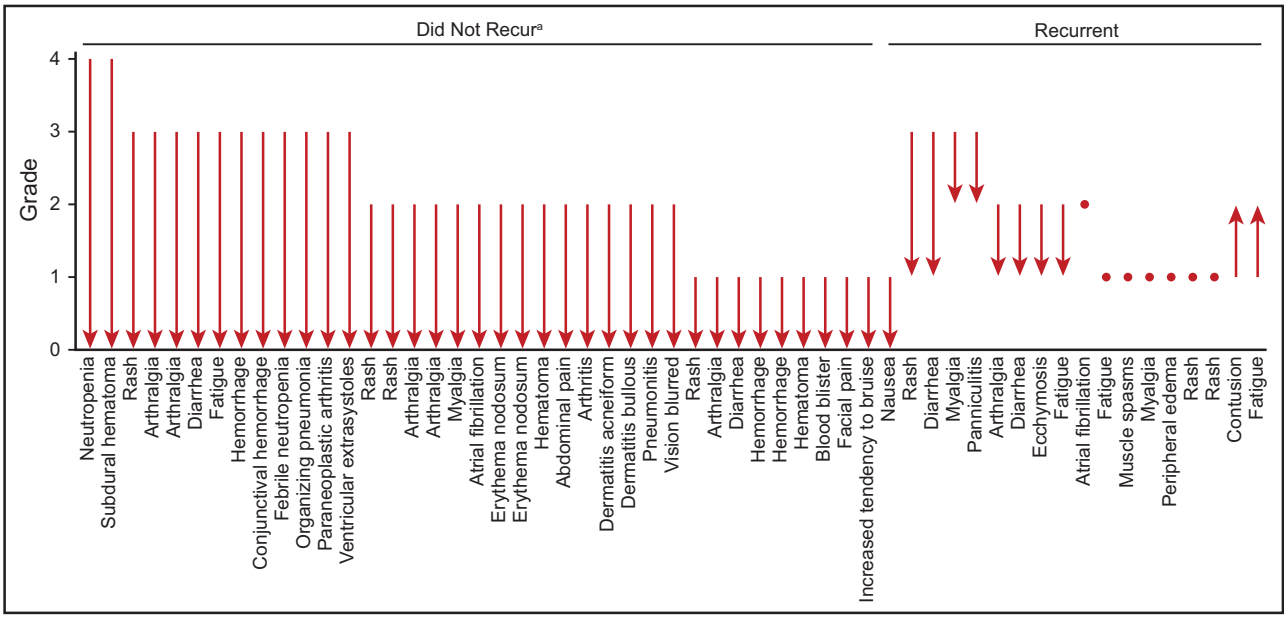

Figure 2. Change in ibrutinib-related adverse events during acalabrutinib treatment. [a]An additional 6 events of unknown grade (rash, diarrhea, hemorrhage, decreased appetite, dyspnea, and weight decreased) did not recur. Reprinted with permission from Awan et al. .[50] Copyright © 2019 The American Society of Hematology.

Zanubrutinib received FDA approval in 2021 for treating adult patients with WM, based on results from the phase III ASPEN trial (BGB-3111-302; NCT03053440).[52,59] ASPEN was a prospective, randomized, open-label trial in WM, comparing zanubrutinib vs. ibrutinib in 201 patients with WM (patients with prior BTK inhibitor exposure were excluded from the study).[60] Although the primary endpoint of complete response/very good partial response (CR/VGPR) superiority with zanubrutinib vs. ibrutinib was not met, at a median follow-up of 19 months, responses (CR + VGPR) generally favored zanubrutinib vs. ibrutinib across a broad range of patients with WM (26% vs. 17% of treatment-naïve patients and 29% vs. 20% of R/R patients had VGPR). Among patients who had a CR/VGPR, a higher proportion of those treated with zanubrutinib (93%) vs. ibrutinib (64%) was event free at 18 months. In addition, zanubrutinib demonstrated lower rates and severity of BTK inhibitor-associated cardiovascular AEs vs. ibrutinib (2% vs. 15% of patients experienced atrial fibrillation events). Among all AEs, atrial fibrillation, diarrhea, contusion, muscle spasms, peripheral edema, and pneumonia occurred at a ≥10% higher rate in patients treated with ibrutinib vs. zanubrutinib. Only neutropenia was reported at a ≥10% higher rate in patients treated with zanubrutinib.

Zanubrutinib in Ibrutinib-Intolerant Patients With Relapsed/Refractory B-Cell Malignancies

There is an ongoing (at the time of writing) phase II, single-arm, open-label study (NCT04116437) evaluating zanubrutinib in patients with B-cell malignancies who are intolerant of prior BTK inhibitor therapy (either prior ibrutinib [cohort 1] or prior acalabrutinib ± ibrutinib [cohort 2]).[61] Interim data were available from 57 patients in cohort 1 who had CLL/SLL (n = 44), WM (n = 9), MCL (n = 2), and MZL (n = 2). Seven patients were enrolled in cohort 2 (4 patients with CLL, and 1 each with WM, MCL, or MZL), of which 5 were intolerant of both ibrutinib and acalabrutinib. The median follow-up duration for this analysis was 9 months. The median age in both cohorts was 71 years (range, 49-91 years in cohort 1 and 65-76 years in cohort 2). The median duration of treatment in cohort 1 was 8.7 months (range, 0.6-17.9 months) and 8.2 months (range, 6.4-11.4 months) in cohort 2. The most frequently reported AEs with zanubrutinib (incidence ≥ 20%) were contusion/bruising (22%) and fatigue (21%). The most common grade ≥ 3 AEs (incidence > 1 patient) with zanubrutinib were neutropenia (12%) and syncope (3%). Overall, 73% of patients did not experience recurrence of their ibrutinib- or acalabrutinib-related intolerance events, and 79% of AEs that did recur with zanubrutinib treatment did so at lower severity, even among the AEs common to ibrutinib, such as hypertension, rash, atrial fibrillation, arthralgia, and hemorrhage (Fig. 3).

Switching Costs

It is important to note that while switching from ibrutinib to another BTK inhibitor may improve patient outcomes and/or quality of life, there may be extra costs involved in switching therapies. Several studies have compared the economic outcomes of receiving ibrutinib vs. other BTK inhibitors. One study, which modeled the cost-effectiveness of ibrutinib vs. acalabrutinib vs. zanubrutinib in data from 3 clinical trials studying patients with R/R MCL, found that the incremental cost of treatment was highest with acalabrutinib, followed by zanubrutinib, and lowest with ibrutinib.[62] However, the additional cost of the next-generation BTK inhibitors was accompanied by a PFS benefit, which made acalabrutinib the preferred treatment option within a $150 000 patient willingness-to-pay (WTP) constraint, when normalized by the additional cost to gain 1 life-year of PFS. The study found that both acalabrutinib and zanubrutinib were cost-effective against a WTP threshold of $150 000, and that acalabrutinib was 59% likely to be cost-effective while zanubrutinib was 41% likely to be cost-effective. In a different analysis, the cost-effectiveness of ibrutinib vs. zanubrutinib in patients with WM from a US payer perspective was compared, and it

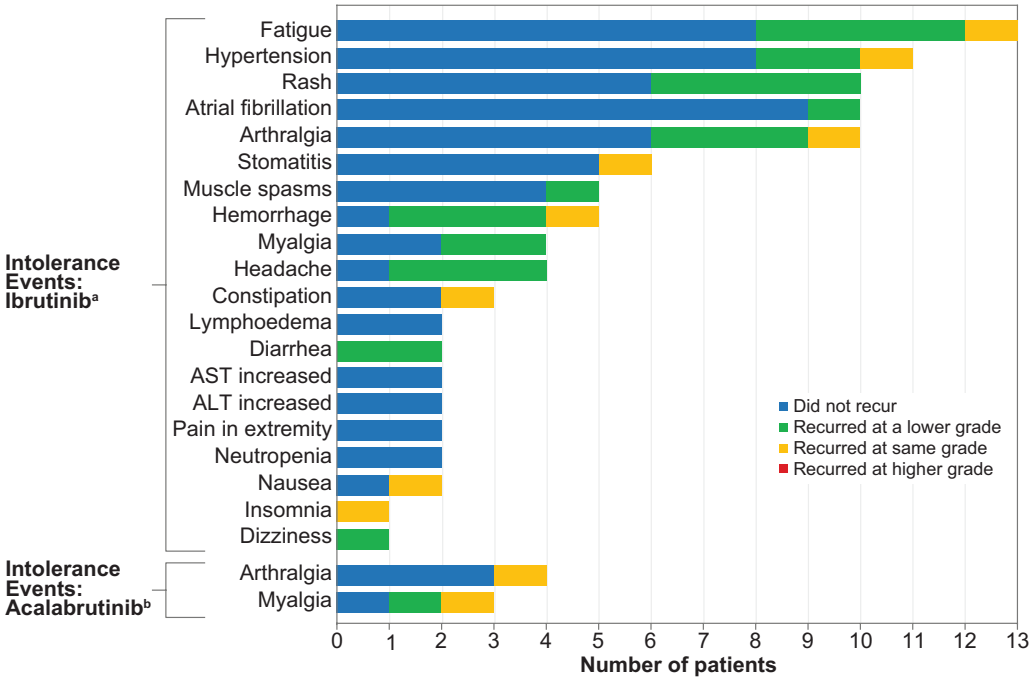

Figure 3. Recurrence of ibrutinib and acalabrutinib intolerance events in patients treated with zanubrutinib. [a]18 ibrutinib intolerance events (arthritis, bone pain, bronchitis, embolism, heart rate irregular, malaise, pericardial effusion, pleural effusion, pneumonia, psoriasis, pyrexia, sinusitis, subcutaneous abscess, supraventricular tachycardia, transaminases increased, ventricular extrasystoles, vertigo, and vomiting) occurred in 1 patient and did not recur on zanubrutinib. [b]11 acalabrutinib intolerance events (abdominal pain, asthenia, atrial fibrillation, dyspepsia, fatigue, groin pain, headache, insomnia, malaise, pain in extremity, and rash) occurred in 1 patient and did not recur on zanubrutinib (not shown in figure). Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase. Reprinted with permission from Shadman et al.[61] Copyright © 2021 American Society of Hematology. Published by Elsevier Inc.

was found that while the overall cost of zanubrutinib treatment was higher, this was offset by the fact that zanubrutinib had a lower monthly drug acquisition, reduced cost of routine and terminal care, and patients stayed on zanubrutinib treatment longer because it had a longer time to treatment failure.[63] Zanubrutinib was also found to be 61% likely to be cost-effective at a WTP threshold of $100 000. Finally, according to a study investigating the cost-effectiveness of first-line vs. third-line ibrutinib in patients with CLL, the cost of ibrutinib would need to be decreased by 72% for first-line ibrutinib therapy to be cost-effective against the WTP threshold of $150 000.[64] According to these studies, the increase in the cost of next-generation BTK inhibitors compared with ibrutinib is within most patients' WTP threshold, and benefits in efficacy and quality of life may justify the increased cost for many patients.

Strategy 3: Abandon Covalent BTK Inhibitor Therapy

Guidelines for the treatment of B-cell malignancies provide a wealth of information to clinical decision makers; however, the data are not sufficiently granular to provide guidance in the ibrutinib-intolerant setting. As with many rare diseases, enrollment in a clinical trial could offer disease control and will help improve the therapeutic landscape for future patients. There are several ongoing trials investigating non-covalent BTK inhibitors in B-cell malignancies (Table 3).

If clinical trial enrollment is not possible, other standard treatment options are suggested for ibrutinib-intolerant patients with previously treated B-cell malignancies.[17-19] Rituximab-based combination therapies, such as bendamustine + rituximab[65,66] or rituximab-bortezomib-dexamethasone[67] are commonly used in R/R patients with B-cell malignancies (ie, CLL and MCL) and may be an appropriate strategy for the ibrutinib-intolerant setting, especially in patients who have not yet been exposed to these regimens. The findings from a study in patients with WM and acquired resistance to ibrutinib monotherapy given salvage therapy (ie, bendamustine + rituximab, proteasome inhibitors + dexamethasone + rituximab, and fludarabine + rituximab) showed that response to salvage treatment was associated with better OS (hazard ratio, 0.08; 95% CI, 0.02-0.38). In addition, this study found that continuation of ibrutinib treatment until subsequent treatment began (bridging) was important for improving disease control and clinical outcomes; patients who had a gap of >7 days prior to receiving salvage therapy were more likely to experience a serum IgM rebound and symptomatic hyperviscosity than patients who received subsequent therapy within 7 days of stopping ibrutinib (76% vs 29%).[68]

Although not currently FDA approved for WM, MCL, or MZL, the BCL2 antagonist venetoclax (currently approved for CLL/SLL[69]) is another treatment option that has been evaluated in B-cell malignancies. In a phase I first-in-human study (NCT01328626) of venetoclax in patients with R/R non-Hodgkin lymphoma (including follicular lymphoma [FL; n = 29], MCL [n = 28], MZL [n = 3], WM [n = 4], and diffuse large B-cell lymphoma [n = 41]), long-term follow-up (median of 38.5 months) showed that overall responses were achieved in 38% of patients with FL, 75% with MCL, 67% with MZL, and 100% with WM.[70] Complete remission occurred in patients with FL (17%) and MCL (21%). The most common AEs reported in the first year were nausea (53%), diarrhea (47%), fatigue (34%), upper respiratory

Table 3. Ongoing clinical trials investigating non-covalent BTK inhibitors.

Indication	Trial number	Phase	BTK inhibitor
WM	NCT03162536	I/II	Nemtabrutinib
	NCT03740529	I/II	Pirtobrutinib
	NCT05176691	I	HMPL-760
	NCT05172700	Expanded access program	Pirtobrutinib
MZL	NCT03740529	I/II	Pirtobrutinib
	NCT05176691	I	HMPL-760
MCL	NCT04662255	III	Pirtobrutinib
	NCT03740529	I/II	Pirtobrutinib
	NCT05458297	II	Nemtabrutinib
	NCT05172700	Expanded access program	Pirtobrutinib
	NCT05176691	I	HMPL-760
CLL/SLL	NCT05172700	Expanded access program	Pirtobrutinib
	NCT04666038	III	Pirtobrutinib
	NCT05023980	III	Pirtobrutinib
	NCT04965493	III	Pirtobrutinib
	NCT03740529	I/II	Pirtobrutinib
	NCT05254743	III	Pirtobrutinib
	NCT05458297	II	Nemtabrutinib
	NCT05176691	I	HMPL-760
	NCT05365100	I/II	BN102
	NCT03893682	I	CG-806
	NCT04305444	II	DTRM-555

Abbreviations: BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenström macroglobulinemia.

tract infections (23%), neutropenia (19%), anemia (17%), and thrombocytopenia (15%), and the incidence of all AEs decreased over time.

A phase II study of venetoclax monotherapy (NCT02677324)[71,72] enrolled 32 patients with previously treated WM, of whom 16 were previously treated with BTK inhibitors. The data suggested that patients with prior BTK inhibitor exposure had a longer time to respond than patients without prior BTK inhibitor exposure (4.5 vs. 1.4 months; $P < .001$). Frequently reported AEs (incidence ≥3 events) included neutropenia (17 events), anemia (8 events), lymphopenia (6 events), nausea (4 events), diarrhea (3 events), and upper respiratory tract infection (3 events). The only recurring grade ≥3 AE was neutropenia ($n = 14$; 45%), including one episode of febrile neutropenia.

Future Directions

Several clinical trials in progress are evaluating the efficacy and safety of novel agents such as non-covalent BTK inhibitors, antibody–drug conjugates, phospholipid–drug conjugates, chimeric antigen receptor T cells (CAR T cells), and BCL2 inhibitors. Given the impact BTK inhibition has had on the treatment landscape, combinations with chemotherapeutic agents, proteasome inhibitors, BCL2 antagonists, and anti-CD38 antibodies appear to be the logical next step in the treatment paradigm. Non-covalent BTK inhibitors are of great interest, as these agents may overcome the mechanisms of resistance that affect the efficacy of covalent BTK inhibitors. For example, pirtobrutinib is a non-covalent BTK inhibitor that has demonstrated efficacy and safety in a phase I/II multicenter study in patients with advanced B-cell malignancies who received > 2 prior therapies. In the trial (NCT03740529), 323 patients were treated across 7 dose levels of pirtobrutinib (25-300 mg once daily). In 19 patients with WM in whom efficacy was evaluable, the ORR was 68% (ORR was 69% in the 13 patients who had received a previous covalent BTK inhibitor). The frequency of AEs commonly associated with BTK inhibition occurred at a diminished rate with pirtobrutinib therapy, and grade 3 atrial fibrillation/flutter was not observed in any patient.[73] Another non-covalent BTK inhibitor, nemtabrutinib, has shown increased survival in CLL animal models compared with ibrutinib, has shown efficacy in a phase I trial of patients with relapsed/refractory B-cell malignancies,[74] and is currently in clinical trials for patients with WM. Other potential pathways of interest include phosphoinosito-3-kinase (PI3K), programmed cell death 1 protein/programmed cell death 1 ligand 1 (PD-1/PD-L1), C-X-C chemokine receptor type 4 (CXCR4), and hemopoietic cell kinase (HCK). We strongly recommend the thoughtful design of clinical trials in treatment-naïve patients as well as those who are refractory to or intolerant of ibrutinib aimed not only at improving response and survival but also the quality of life.

Summary

Three strategies have been described herein to address ibrutinib intolerance in patients with B-cell malignancies. In some cases, addressing the side effects of ibrutinib while maintaining ibrutinib treatment (possibly with treatment pause and/or dose reduction) may be the best option. Clinical trials have also shown that some patients respond well to switching to other, next-generation, irreversible BTK inhibitors acalabrutinib or ibrutinib. Still, others may respond best to switching to other types of therapy, including non-covalent BTK inhibitors (such as pirtobrutinib or nemtabrutinib), chemotherapy (such as rituximab-based chemoimmunotherapies), or BCL2 inhibitors (such as venetoclax). It is our opinion that you chose the approach that best works with your patient's needs.

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Conflict of Interest

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Author Contributions

All authors contributed to conception, writing, and final approval of the manuscript.

Data Availability

No new data were generated or analyzed in support of this research.

References

1. Hendriks RW, Yuvaraj S, Kil LP. Targeting Bruton's tyrosine kinase in B cell malignancies. *Nat Rev Cancer*. 2014;14(4):219-232.
2. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. *Mol Cancer*. 2018;17(1):57.
3. *Imbruvica (ibrutinib) [package insert]*. Pharmacyclics LLC; 2019.
4. Castillo JJ, Advani RH, Branagan AR, et al. Consensus treatment recommendations from the tenth International Workshop for Waldenström Macroglobulinaemia. *Lancet Haematol*. 2020;7(11):e827-e837.
5. Yin X, Chen L, Fan F, et al. Trends in incidence and mortality of Waldenström macroglobulinemia: a population-based study. *Front Oncol*. 2020;10:1712.
6. Kristinsson SY, Eloranta S, Dickman PW, et al. Patterns of survival in lymphoplasmacytic lymphoma/Waldenström macroglobulinemia: a population-based study of 1,555 patients diagnosed in Sweden from 1980 to 2005. *Am J Hematol*. 2013;88(1):60-65.
7. Wang W, Lin P. Lymphoplasmacytic lymphoma and Waldenström macroglobulinaemia: clinicopathological features and differential diagnosis. *Pathology*. 2020;52(1):6-14. https://doi.org/10.1016/j.pathol.2019.09.009.
8. Hanel W, Epperla N. Emerging therapies in mantle cell lymphoma. *J Hematol Oncol*. 2020;13(1):79.
9. *Mantle Cell Lymphoma Facts*. The Leukemia & Lymphoma Society website. Accessed September 2022. https://www.lls.org/sites/default/files/file_assets/mantlecelllymphoma.pdf.
10. Lynch DT, Koya S, Acharya U. *Mantle Cell Lymphoma*. StatPearls; 2022.
11. Zucca E, Arcaini L, Buske C, et al. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(1):17-29. https://doi.org/10.1016/j.annonc.2019.10.010.
12. Cerhan JR, Habermann TM. Epidemiology of marginal zone lymphoma. *Ann Lymphoma*. 2021;5:1-1. https://doi.org/10.21037/aol-20-28.
13. Sindel A, Al-Juhaishi T, Yazbeck V. Marginal zone lymphoma: state-of-the-art treatment. *Curr Treat Options Oncol*. 2019;20(12):90.
14. Zelenetz AD, Gordon LI, Wierda WG, et al. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2015. *J Natl Compr Canc Netw*. 2015;13(3):326-362.
15. Hallek M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment. *Am J Hematol*. 2019;94(11):1266-1287. https://doi.org/10.1002/ajh.25595.
16. Sarosiek S, Sermer D, Branagan AR, Treon SP, Castillo JJ. Zanubrutinib for the treatment of adults with Waldenstrom macroglobulinemia. *Expert Rev Anticancer Ther*. 2022;22(5):471-478. https://doi.org/10.1080/14737140.2022.2064849.
17. National Comprehensive Cancer Network. *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 1.2023)*. Accessed September 8, 2022. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/; https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.
18. National Comprehensive Cancer Network. *Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma (Version 1.2023)*. Accessed September 8, 2022. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/; https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf.
19. National Comprehensive Cancer Network. *B-Cell Lymphomas (Version 5.2022)*. Accessed September 8, 2022. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/; https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.
20. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. *N Engl J Med*. 2015;372(15):1430-1440. https://doi.org/10.1056/nejmoa1501548.
21. Castillo JJ, Meid K, Gustine JN, et al. Long-term follow-up of ibrutinib monotherapy in treatment-naive patients with Waldenstrom macroglobulinemia. *Leukemia*. 2022;36(2):532-539.
22. Treon SP, Meid K, Gustine J, et al. Long-term follow-up of ibrutinib monotherapy in symptomatic, previously treated patients with Waldenström macroglobulinemia. *J Clin Oncol*. 2021;39(6):565-575. https://doi.org/10.1200/jco.20.00555.
23. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia. *N Engl J Med*. 2018;378(25):2399-2410. https://doi.org/10.1056/nejmoa1802917.
24. Buske C, Tedeschi A, Trotman J, et al. Ibrutinib plus rituximab versus placebo plus rituximab for Waldenström's macroglobulinemia: final analysis from the randomized Phase III iNNOVATE study. *J Clin Oncol*. 2022;40(1):52-62. https://doi.org/10.1200/jco.21.00838.
25. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2013;369(6):507-516.
26. Noy A, de Vos S, Thieblemont C, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. *Blood*. 2017;129(16):2224-2232. https://doi.org/10.1182/blood-2016-10-747345.
27. Munir T, Brown JR, O'Brien S, et al. 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*. 2019;94(12):1353-1363.
28. Barr PM, Owen C, Robak T, et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv*. 2022;6(11):3440-3450. https://doi.org/10.1182/bloodadvances.2021006434.
29. Fraser GAM, Chanan-Khan A, Demirkan F, et al. Final 5-year findings from the phase 3 HELIOS study of ibrutinib plus bendamustine and rituximab in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leuk Lymphoma*. 2020;61(13):3188-3197.
30. Hou JZ, Ryan K, Du S, et al. Real-world ibrutinib dose reductions, holds and discontinuations in chronic lymphocytic leukemia. *Future Oncol*. 2021;17(35):4959-4969. https://doi.org/10.2217/fon-2021-0964.
31. Parikh SA, Achenbach SJ, Call TG, et al. The impact of dose modification and temporary interruption of ibrutinib on outcomes of chronic lymphocytic leukemia patients in routine clinical practice. *Cancer Med*. 2020;9(10):3390-3399. https://doi.org/10.1002/cam4.2998.

32. Sarosiek S, Gustine J, Flynn CA, et al. Dose reductions related to adverse effects in patients with Waldenström macroglobulinemia treated with the BTK-inhibitor ibrutinib. *Blood*. 2021;138(Supplement 1):3529-3529. https://doi.org/10.1182/blood-2021-154284.
33. de Jong J, Skee D, Murphy J, et al. Effect of CYP3A perpetrators on ibrutinib exposure in healthy participants. *Pharmacol Res Perspect*. 2015;3(4):e00156.
34. Gustine JN, Meid K, Dubeau T, et al. Ibrutinib discontinuation in Waldenström macroglobulinemia: etiologies, outcomes, and IgM rebound. *Am J Hematol*. 2018;93(4):511-517. https://doi.org/10.1002/ajh.25023.
35. Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. *Haematologica*. 2017;102(10):1796-1805. https://doi.org/10.3324/haematol.2017.171041.
36. Paydas S. Management of adverse effects/toxicity of ibrutinib. *Crit Rev Oncol Hematol*. 2019;136:56-63. https://doi.org/10.1016/j.critrevonc.2019.02.001.
37. Stephens DM, Byrd JC. How I manage ibrutinib intolerance and complications in patients with chronic lymphocytic leukemia. *Blood*. 2019;133(12):1298-1307. https://doi.org/10.1182/blood-2018-11-846808.
38. Lipsky AH, Farooqui MZ, Tian X, et al. Incidence and risk factors of bleeding-related adverse events in patients with chronic lymphocytic leukemia treated with ibrutinib. *Haematologica*. 2015;100(12):1571-1578.
39. Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood*. 2015;126(6):739-745. https://doi.org/10.1182/blood-2015-03-635326.
40. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood*. 2015;125(16):2497-2506. https://doi.org/10.1182/blood-2014-10-606038.
41. Iberri DJ, Kwong BY, Stevens LA, et al. Ibrutinib-associated rash: a single-centre experience of clinicopathological features and management. *Br J Haematol*. 2018;180(1):164-166.
42. Mehta HM, Malandra M, Corey SJ. G-CSF and GM-CSF in Neutropenia. *J Immunol*. 2015;195(4):1341-1349. https://doi.org/10.4049/jimmunol.1500861.
43. Brown JR. How I treat CLL patients with ibrutinib. *Blood*. 2018;131(4):379-386. https://doi.org/10.1182/blood-2017-08-764712.
44. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369(1):32-42. https://doi.org/10.1056/nejmoa1215637.
45. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol*. 2013;31(1):88-94.
46. *Calquence (acalabrutinib) [package insert]*. AstraZeneca Pharmaceuticals LP; 2019.
47. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. *J Clin Oncol*. 2021;39(31):3441-3452. https://doi.org/10.1200/jco.21.01210.
48. Owen RG, McCarthy H, Rule S, et al. Acalabrutinib monotherapy in patients with Waldenström macroglobulinemia: a single-arm, multicentre, phase 2 study. *Lancet Haematol*. 2020;7(2):e112-e121.
49. Strati P, Coleman M, Champion R, et al. A phase 2, multicentre, open-label trial (ACE-LY-003) of acalabrutinib in patients with relapsed or refractory marginal zone lymphoma. *Br J Haematol*. 2022;199(1):76-85. https://doi.org/10.1111/bjh.18368.
50. Awan FT, Schuh A, Brown JR, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. *Blood Adv*. 2019;3(9):1553-1562. https://doi.org/10.1182/bloodadvances.2018030007.
51. Rogers KA, Thompson PA, Allan JN, et al. Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia. *Haematologica*. 2021;106(9):2364-2373. https://doi.org/10.3324/haematol.2020.272500.
52. *Brukinsa (zanubrutinib) [package insert]*. BeiGene USA; 2021.
53. Trotman J, Opat S, Gottlieb D, et al. Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: 3 years of follow-up. *Blood*. 2020;136(18):2027-2037. https://doi.org/10.1182/blood.2020006449.
54. Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood*. 2019;134(11):851-859. https://doi.org/10.1182/blood.2019001160.
55. Tam CS, Opat S, Simpson D, et al. Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma. *Blood Adv*. 2021;5(12):2577-2585. https://doi.org/10.1182/bloodadvances.2020004074.
56. Muñoz J, Wang Y, Jain P, et al. Zanubrutinib in lymphoproliferative disorders: a comprehensive review. *Ther Adv Hematol*. 2022;13:1-23.
57. Tam CS, Dimopoulos MA, Garcia-Sanz R, et al. Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. *Blood Adv*. 2021;6(4):1296-1308.
58. Hillmen P, Eichhorst B, Brown JR, et al. *First Interim Analysis of ALPINE Study: Results of a Phase 3 Randomized Study of Zanubrutinib vs Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Abstract]*. EHA Library; 2021; LB1900
59. Tam CS, LeBlond V, Novotny W, et al. A head-to-head Phase III study comparing zanubrutinib versus ibrutinib in patients with Waldenström macroglobulinemia. *Future Oncol*. 2018;14(22):2229-2237. https://doi.org/10.2217/fon-2018-0163.
60. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood*. 2020;136(18):2038-2050. https://doi.org/10.1182/blood.2020006844.
61. Shadman M, Flinn IW, Levy MY, et al. Phase 2 study of zanubrutinib in BTK inhibitor-intolerant patients (Pts) with relapsed/refractory B-Cell malignancies. *Blood*. 2021(Supplement 1);138:1410-1410. https://doi.org/10.1182/blood-2021-148544.
62. Alrawashdh N, McBride A, Slack M, et al. Cost-effectiveness and value of information analyses of Bruton's tyrosine kinase inhibitors in the treatment of relapsed or refractory mantle cell lymphoma in the United States. *J Manag Care Spec Pharm*. 2022;28(4):390-400.
63. Castillo JJ, Yang K, Liu R, et al. Cost-effectiveness of zanubrutinib versus ibrutinib in adult patients with Waldenström macroglobulinemia in the United States. *J Clin Oncol*. 2021;39:15_suppl, e18856-e18856 Abstract. https://doi.org/10.1200/jco.2021.39.15_suppl.e18856.
64. Patel KK, Isufi I, Kothari S, et al. Cost-effectiveness of first-line vs third-line ibrutinib in patients with untreated chronic lymphocytic leukemia. *Blood*. 2020;136(17):1946-1955. https://doi.org/10.1182/blood.2020004922.
65. Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol*. 2011;29(26):3559-3566. https://doi.org/10.1200/jco.2010.33.8061.
66. Iannitto E, Morabito F, Mancuso S, et al. Bendamustine with or without rituximab in the treatment of relapsed chronic lymphocytic leukaemia: an Italian retrospective study. *Br J Haematol*. 2011;153(3):351-357. https://doi.org/10.1111/j.1365-2141.2011.08597.x.
67. Lamm W, Kaufmann H, Raderer M, et al. Bortezomib combined with rituximab and dexamethasone is an active regimen for patients with relapsed and chemotherapy-refractory mantle cell lymphoma. *Haematologica*. 2011;96(7):1008-1014. https://doi.org/10.3324/haematol.2011.041392.

68. Gustine JN, Sarosiek S, Flynn CA, et al. Natural history of Waldenström macroglobulinemia following acquired resistance to ibrutinib monotherapy. *Haematologica*. 2022;107(5):1163-1171.
69. *Venclexta (venetoclax) [package insert]*. AbbVie Inc.; 2020.
70. Davids MS, Roberts AW, Kenkre VP, et al. Long-term follow-up of patients with relapsed or refractory non-hodgkin lymphoma treated with venetoclax in a phase I, first-in-human study. *Clin Cancer Res*. 2021;27(17):4690-4695. https://doi.org/10.1158/1078-0432.ccr-20-4842.
71. Ravi G, Kapoor P. Current approach to Waldenström Macroglobulinemia. *Cancer Treat Res Commun*. 2022;31:100527.
72. Castillo JJ, Allan JN, Siddiqi T, et al. Venetoclax in previously treated Waldenström macroglobulinemia. *J Clin Oncol*. 2021;40(1):63-71.
73. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet*. 2021;397(10277):892-901.
74. Robak T, Witkowska M, Smolewski P. The role of Bruton's kinase inhibitors in chronic lymphocytic leukemia: current status and future directions. *Cancers (Basel)*. 2022;14(3):771.