A Review of the Bruton Tyrosine Kinase Inhibitors in B-Cell Malignancies

DONALD C. MOORE,1 PharmD, BCPS, BCOP, DPLA, and DANIEL THOMPSON,2 PharmD

Abstract

The B-cell receptor signaling pathway plays an integral role in the proliferation and survival of malignant B cells. Targeting the B-cell receptor pathway via the inhibition of Bruton tyrosine kinase (BTK) has evolved the treatment of a variety of B-cell malignancies, including chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone lymphoma, and Waldenström macroglobulinemia. Currently, there are three BTK inhibitors approved by the U.S. Food and Drug Administration: ibrutinib, acalabrutinib, and zanubrutinib. This article reviews the pharmacology, clinical efficacy, safety, dosing, drug-drug interactions, and implications for advanced practitioners of BTK inhibitors in the treatment of B-cell malignancies.

Targeting the B-cell receptor (BCR) signaling pathway has become an area of interest in the development of pharmacotherapy to treat B-cell malignancies. The BCR pathway plays a role in the growth, proliferation, and survival of normal and malignant B cells (Kenkre & Khal, 2012). One of the essential enzymes in the BCR signaling pathway is Bruton tyrosine kinase (BTK). Bruton tyrosine kinase is downstream of BCR. Inhibition of BTK can lead to the downstream mitigation of cell growth, proliferation, adhesion, migration, and survival of malignant B cells (Buggy & Elias, 2012). Targeting the BCR signaling pathway with BTK inhibitors has dramatically evolved the treatment of several B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and Waldenström macroglobulinemia (WM). Currently, there are three BTK inhibitors approved by the U.S. Food & Drug Administration (FDA) for the treatment of B-cell malignancies: ibrutinib (Imbruvica), acalabrutinib (Calquence), and zanubrutinib (Brukinsa). Herein, we review the pharmacology, efficacy, safety, dosing, administration, and implications for advanced practitioners of BTK inhibitors in the treatment of B-cell malignancies.

IBRUTINIB
Ibrutinib is an oral, small-molecule inhibitor of BTK that covalently binds to the cysteine residue on the active site of BTK (Pharmacyclics,
By blocking the enzymatic activity of BTK, ibrutinib inhibits the proliferation and survival of malignant B-cells. Ibrutinib is indicated for the treatment of several B-cell malignancies, including CLL, MCL, MZL, and WM (Table 1). Additionally, ibrutinib is also approved for the treatment of chronic graft-vs.-host disease after patients have failed one or more lines of systemic therapy; however, this is outside the scope of this article. For the treatment of CLL/SLL and WM, ibrutinib is dosed as 420 mg orally once daily. Ibrutinib is dosed as 560 mg orally once daily for MCL and MZL.

### Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Ibrutinib has been evaluated for the treatment of CLL in numerous studies, both in the previously untreated and relapsed/refractory settings.

The phase III RESONATE trial randomized 391 patients with relapsed/refractory CLL/SLL to receive either ibrutinib 420 mg orally daily until disease progression or ofatumumab (Kesimpta; Byrd et al., 2014). Patients in the ibrutinib and ofatumumab arms had received a median of three and two prior lines of therapy, respectively. Ibrutinib significantly prolonged the primary endpoint of median progression-free survival (PFS) compared with ofatumumab (44.1 vs. 8.1 months; hazard ratio [HR], 0.148, 95% confidence interval [CI] = 0.113–0.196, p < .001). The 6-year follow-up data of the trial demonstrated an overall response rate (ORR) of 91% with ibrutinib (Munir et al., 2019).

Ibrutinib has been compared with chemotherapy regimens in older patients with previously untreated CLL in three phase III trials: RESONATE-2, iLLUMINATE, and A041202. The RESONATE-2 trial randomized 269 patients who were 65 years of age or older with untreated CLL to ibrutinib 420 mg orally daily until disease progression or chlorambucil (Burger et al., 2020). Patients with del17p were excluded. The primary endpoint of PFS was significantly improved with ibrutinib compared with chlorambucil (median, not reached [NR] vs. 15.0 months; HR, 0.16, 95% CI = 0.10–0.29). As a secondary endpoint, ibrutinib also improved the 5-year overall survival (OS) rate compared with chlorambucil (83% vs. 68%; HR, 0.45, 95% CI = 0.26–0.76).

| Table 1. Summary of FDA-Approved BTK Inhibitors |
|-----------------------------------------------|
| **Approved indications**                     | **Ibrutinib** | **Acalabrutinib** | **Zanubrutinib** |
| • CLL/SLL                                     | • CLL/SLL     | • MCL in patients who have received at least one prior therapy | • MCL in patients who have received at least one prior therapy |
| • CLL/SLL with 17p deletion                   | • MCL in patients who have received at least one prior therapy | • MCL/SLL            | • MCL in patients who require systemic therapy and have a received at least one prior anti-CD20-based therapy |
| • WM                                          | • CLL/SLL     | • MCL in patients who have received at least one prior therapy | • Chronic GVHD       |
| • MCL in patients who have received at least one prior therapy | • MCL in patients who have received at least one prior therapy | • MCL in patients who have received at least one prior therapy | • MCL in patients who have received at least one prior therapy |
| • MZL in patients who require systemic therapy and have a received at least one prior anti-CD20-based therapy | • MCL in patients who have received at least one prior therapy | • MCL in patients who have received at least one prior therapy | • MCL in patients who have received at least one prior therapy |
| • Chronic GVHD                                | • MCL in patients who have received at least one prior therapy | • MCL in patients who have received at least one prior therapy | • MCL in patients who have received at least one prior therapy |

| Dosage forms | **Ibrutinib** | **Acalabrutinib** | **Zanubrutinib** |
|--------------|---------------|-------------------|-----------------|
| 70-mg and 140-mg capsules; 140-mg, 280-mg, 420-mg, and 560-mg tablets | 100-mg capsules | 80-mg capsules |
| Dosing and administration | **CLL/SLL and WM: 420 mg orally once daily** | **MCL and MZL: 560 mg orally once daily** | **100 mg orally every 12 hours, taken with or without food** |
| Warnings and precautions | **Hemorrhage, infections, cytopenias, cardiac arrhythmias, hypertension, second primary malignancies, tumor lysis syndrome, embryo-fetal toxicity** | **Serious and opportunistic infections, hemorrhage, cytopenias, second primary malignancies, atrial fibrillation and flutter** | **Hemorrhage, infections, cytopenias, cardiac arrhythmias, embryo-fetal toxicity** |

Note. CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; GVHD = graft-vs.-host disease; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; WM = Waldenström macroglobulinemia.
The iLLUMINATE trial randomized older patients (age ≥ 65) or younger patients with coexisting conditions with previously untreated CLL to receive either obinutuzumab (Gazyva) and ibrutinib or obinutuzumab and chlorambucil (Moreno et al., 2019). Median PFS was significantly prolonged with obinutuzumab and ibrutinib compared with obinutuzumab and chlorambucil (NR vs. 19 months; HR, 0.23, 95% CI = 0.15–0.37, p < .001). In a subgroup analysis, patients with high-risk CLL-related features (del17p, del11q, TP53 mutations, or unmutated IgHV) also had significantly improved PFS in the ibrutinib arm compared with chemoimmunotherapy (median NR vs. 14.7 months; HR, 0.15, 95% CI = 0.09–0.27, p < .001).

The A041202 trial randomized 547 older patients (age ≥ 65) with previously untreated CLL to receive either ibrutinib, ibrutinib and rituximab, or bendamustine and rituximab (Woyach et al., 2018). The 2-year PFS was higher with both ibrutinib alone (87%; HR, 0.39, 95% CI = 0.26–0.58, p < .001) and ibrutinib and rituximab (88%; HR, 0.38, 95% CI = 0.25–0.59, p < .001) compared with bendamustine and rituximab (74%). The ORR with ibrutinib, ibrutinib and rituximab, and bendamustine and rituximab were 93%, 94%, and 81%, respectively. No significant differences between PFS and ORR between the two ibrutinib groups in the trial were noted.

The open-label, randomized phase III E1912 trial evaluated ibrutinib plus rituximab to fludarabine, cyclophosphamide, and rituximab (FCR) for the treatment of previously untreated CLL in patients 70 years of age or younger (Shanafelt et al., 2019). Patients randomized to the ibrutinib-containing arm received ibrutinib 420 mg orally once daily until disease progression or toxicity and rituximab once every 28 days for 6 doses. Patients with del17p were excluded due to the historically poor response this population has with FCR. The primary endpoint was PFS; OS was a secondary endpoint. A total of 529 patients were randomized in this study. More patients achieved 3-year PFS with ibrutinib plus rituximab compared with FCR (89.4% vs. 72.9%; HR, 0.35, 95% CI = 0.22–0.56, p < .001). 3-year OS was improved with ibrutinib plus rituximab compared with FCR (98.8% vs. 91.5%; HR, 0.17, 95% CI = 0.05–0.54, p < .001). Patients in each arm experienced similar rates of grade ≥ 3 adverse events (80.1% vs. 79.7%), but patients receiving ibrutinib and rituximab had fewer grade ≥ 3 infectious complications compared with patients receiving FCR (10.5% vs. 20.3%).

Mantle Cell Lymphoma
Ibrutinib’s approval for use in relapsed MCL is based on the results of an open-label, randomized, phase III RAY trial that compared ibrutinib to temsirolimus for the treatment of patients with relapsed/refractory MCL who had received at least one prior chemoimmunotherapy regimen (Rule et al., 2018). The primary endpoint of median PFS was significantly prolonged with ibrutinib compared with temsirolimus (15.6 vs. 6.2 months; HR, 0.45, 95% CI = 0.35–0.60, p < .001). The ORR was higher with ibrutinib than with temsirolimus (77% vs. 46%, p < .001). However, there was no statistically significant difference between ibrutinib and temsirolimus with respect to OS (30 vs. 24 months; p = .06).

Marginal Zone Lymphoma
Ibrutinib was evaluated for the management of previously treated MZL in an open-label phase II trial (Noy et al., 2017). Patients received ibrutinib 560 mg orally once daily until disease progression or intolerable toxicity. Eligible patients had to have received at least one prior line of therapy, including at least one line of therapy consisting of anti-CD20 monoclonal antibody-based therapy (either as monotherapy or chemoimmunotherapy). The primary endpoint was ORR. Secondary endpoints included duration of response and PFS. A total of 63 patients were enrolled in the study. Patients had received a median of two prior lines of therapy. Forty-eight percent of patients achieved a response with ibrutinib. At a median follow-up of 19.4 months, the PFS was 14.2 months and the median duration of response has not yet been reached.

Waldenström Macroglobulinemia
The approval of ibrutinib for WM hallmarked the first FDA approval of a drug for this rare hematologic malignancy. Ibrutinib has been evaluated for the treatment of WM in both the front-line and relapsed/refractory settings. A single-arm, phase II trial evaluated ibrutinib 420 mg orally...
daily in 63 patients with previously treated WM (Treon et al., 2015). Patients had received a median of two prior lines of therapy. The primary objective of ORR was achieved in 90.5% of patients. Following treatment with ibrutinib, median serum IgM levels decreased from 3,520 mg/dL to 880 mg/dL. The 2-year PFS and OS were 69.1% and 95.2%, respectively.

Following the phase II results, ibrutinib was then evaluated in a randomized phase III trial in patients with previously untreated WM (Dimpopoulos et al., 2018). A total of 150 patients were randomized to receive either ibrutinib plus rituximab or rituximab plus placebo. The 30-month PFS rate was significantly improved with ibrutinib and rituximab compared with rituximab alone (92% vs. 47%; p < .001). The addition of ibrutinib to rituximab was also associated with a lower incidence of grade 3/4 infusion-related reactions (1% vs. 16%) and IgM flare (8% vs. 47%).

**ACALABRUTINIB**

Acalabrutinib is an oral, potent, highly selective, second-generation, covalent BTK inhibitor (AstraZeneca Pharmaceuticals LP, 2019). Compared with ibrutinib, acalabrutinib exerts greater selectivity for BTK than other, off-target kinases such as EGFR, TEC, and interleukin-2-inducible T-cell kinase. Due to this difference in off-target effects, it is thought that acalabrutinib may have a lower frequency of adverse events associated with off-target inhibition of non-BTK kinases compared with ibrutinib. Acalabrutinib is currently FDA approved for CLL/SLL and MCL for patients who have had at least one prior line of therapy. The recommended initial dose of acalabrutinib is 100 mg orally twice daily.

**Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma**

The phase III ELEVATE-TN trial evaluated acalabrutinib in patients with treatment-naive CLL (Sharman et al., 2020). Patients were randomized to receive either acalabrutinib, acalabrutinib plus obinutuzumab, or chlorambucil plus obinutuzumab. Patients randomized to the acalabrutinib arms received acalabrutinib 100 mg orally twice daily until disease progression or intolerable toxicity. The primary endpoint was PFS; median OS was a secondary endpoint. A total of 535 patients were randomized in this trial. Acalabrutinib plus obinutuzumab significantly prolonged PFS compared with chemoimmunotherapy (median NR vs. 22.6 months; HR, 0.10, 95% CI = 0.06–0.17, p < .0001). Acalabrutinib monotherapy also led to significant prolongation of PFS over chlorambucil plus obinutuzumab (median NR vs. 22.6 months; HR, 0.20, 95% CI = 0.13–0.30, p < .0001). Median OS was NR in any groups.

The phase III ASCEND trial evaluated acalabrutinib compared with investigator’s choice in patients with relapsed/refractory CLL (Ghia et al., 2019). Patients were randomized to receive either acalabrutinib 100 mg orally twice daily (n = 155) or to either rituximab and idelalisib (Zydelig; n = 119) or rituximab and bendamustine (n = 36). Acalabrutinib significantly prolonged the primary endpoint of PFS compared with the control treatment (median NR vs. 16.5 months; HR, 0.31, 95% CI = 0.20–0.49, p < .0001). Median OS has not been reached for either group. The ORR was not significantly different between acalabrutinib and the control group (81% vs. 75%; p = .22). A significantly higher proportion of patients experienced treatment discontinuation due to an adverse event with idelalisib compared with acalabrutinib (49% vs. 11%). The ASCEND trial is an important study, as it is one of the first to compare head-to-head two different small-molecule inhibitors in CLL (idelalisib and acalabrutinib).

**Mantle Cell Lymphoma**

The ACE-LY-004 trial was an open-label, single-arm, phase II study that evaluated the efficacy and safety of acalabrutinib for the treatment of relapsed/refractory MCL (Wang et al., 2018). Patients received acalabrutinib 100 mg orally twice daily until disease progression or intolerable toxicity. Included patients had to relapse after or have refractory disease to at least one prior therapy and could have had up to five prior lines of treatment. The primary endpoint was ORR. Secondary endpoints included PFS and OS. A total of 124 patients were enrolled in this
study. Patients had a median of two prior lines of treatment. An overall response was achieved in 100 patients (81%); complete response (CR) was achieved in 49 patients (40%). At the median follow-up of 15.2 months, OS and PFS had not yet been reached. At 12 months, OS and PFS were 87% (95% CI = 79%–92%) and 67% (95% CI = 58%–75%), respectively. The authors concluded that a high proportion of patients with relapsed/refractory MCL responded to acalabrutinib.

**ZANUBRUTINIB**

Zanubrutinib is a second-generation, small-molecule inhibitor of BTK. It inhibits BTK activity by forming a covalent bond with a cysteine residue in the BTK active site, similar to the mechanisms of action of ibrutinib and acalabrutinib (BeiGene USA Inc., 2019). Zanubrutinib is currently approved for the treatment of adult patients with MCL who have received at least one prior line of therapy. This indication is currently under accelerated approval by the FDA based on the ORR observed in an open-label, single-arm, phase II trial. Zanubrutinib is dosed as either 160 mg orally twice daily or 320 mg orally once daily.

**Mantle Cell Lymphoma**

The approval of zanubrutinib for the treatment of relapsed/refractory MCL is based on the results of an open-label, single-arm, phase II trial (Song et al., 2019). Patients received zanubrutinib 160 mg orally twice daily until disease progression or intolerable toxicity. The primary endpoint was ORR; a key secondary endpoint was PFS. A total of 86 patients were included in the study. Patients had received a median of two prior lines of therapy. The ORR was 84.7% and the CR rate was 76.5%. The median PFS was 16.7 months. The authors concluded that zanubrutinib was highly active in the treatment of relapsed/refractory MCL.

**IMPLICATIONS FOR THE ADVANCED PRACTITIONER**

**Bleeding and Hemorrhage**

One of the most common adverse events associated with the BTK inhibitors is bleeding. Increased risk of bleeding with the BTK inhibitors occurs from both on-target and off-target effects (Stephens & Byrd, 2019). BTK plays a role in glycoprotein-mediated platelet signaling, adhesion, and aggregation (Liu et al., 2006). Inhibition of BTK can thereby lead to the inhibition of platelet aggregation. With ibrutinib, the off-target effect of TEC kinase inhibition can also play a role in causing bleeding.

Use of concomitant antithrombotic agents with BTK inhibitors can further increase the risk for major bleeding. This can pose a therapeutic challenge particularly as there is an increased risk for atrial fibrillation with BTK inhibitors that can warrant stroke prophylaxis. Concomitant use of warfarin should be avoided with BTK inhibitors; this is a common exclusion criterion in many BTK inhibitor clinical trials, as the concomitant use of warfarin with ibrutinib can increase the risk for subdural hematomas (Wang et al., 2013).

Due to the disruption of platelet aggregation by BTK inhibitors, it is recommended that all BTK inhibitors be held for at least 3 to 7 days before and after surgery.

**Atrial Fibrillation**

Therapy with ibrutinib, acalabrutinib, and zanubrutinib can increase the risk for the development of atrial fibrillation. Risk factors for developing atrial fibrillation with BTK inhibitors include history of hypertension, history of cardiac arrhythmias, and acute infection (AstraZeneca Pharmaceuticals LP, 2019; Pharmacyclics, 2018).

Ibrutinib-induced atrial fibrillation has been reported to occur in up to 10% of patients; however, the incidence has been variable in clinical trials, likely owing to differences in patient populations and ages, as the risk of atrial fibrillation with ibrutinib increases with age (Stephens & Byrd, 2019). The median time to onset is 2.8 months with ibrutinib. The prevalence of this adverse event is the highest in the first 3 months of treatment; however, events have been reported to occur later in therapy.

Atrial fibrillation with ibrutinib may occur secondary to off-target cardiac phosphoinositide 3-kinase inhibition (Stephens & Byrd, 2019). The incidence of atrial fibrillation appears to be higher with ibrutinib compared with acalabrutinib and zanubrutinib; however, this has yet to be validated in head-to-head prospective, randomized, controlled trials.
If atrial fibrillation occurs with a BTK inhibitor, multidisciplinary collaboration with cardiology should be pursued. Rate and rhythm control should be instituted as clinically necessary. Antithrombotic prophylaxis should also be considered in patients at a high risk for stroke. Given the increased risk of bleeding and hemorrhage with the BTK inhibitors, the benefit of antithrombotic prophylaxis should be weighed against the risk of serious bleeding and the need to continue the BTK inhibitor and change to alternative therapy for the underlying B-cell malignancy. Although not validated in the setting of BTK inhibitor-induced atrial fibrillation, scoring systems such as CHA₂DS₂-VASc and HAS-BLED can be used to determine the risk of thrombosis and the risk of bleeding, respectively.

**Hypertension**
The development of hypertension has been reported with the BTK inhibitors. All-grade and high-grade hypertension have been reported to occur in up to 19% and 8% of patients, respectively, receiving ibrutinib (Pharmacyclics, 2018). The prevalence of ibrutinib-induced hypertension appears to increase over time (Coutre et al., 2019). High-grade hypertension has been reported in 2% and 3.4% of patients receiving acalabrutinib and zanubrutinib, respectively (BeiGene USA Inc., 2019; Sharman et al., 2020).

A recent, large retrospective analysis (n = 562) conducted by Dickerson and colleagues (2019) found that 78% of patients initiating ibrutinib developed new or worsening hypertension. New or worsening hypertension secondary to ibrutinib was also associated with an increased risk of major adverse cardiovascular events (Dickerson et al., 2019). Given this potential for cardiovascular morbidity, it is important to monitor for and manage BTK inhibitor-induced hypertension appropriately. Patients receiving a BTK inhibitor should have their blood pressure assessed at baseline and periodically throughout treatment. If hypertension develops in the setting of BTK inhibitor therapy, it should be managed with antihypertensives. There is no single antihypertensive drug class preferred in this setting and selection can be based on other patient-specific factors such as comorbidities.

**Infectious Complications**
Ibrutinib, acalabrutinib, and zanubrutinib all have warnings regarding the risk of serious bacterial, fungal, and viral infectious complications. Opportunistic infections including hepatitis B reactivation, Pneumocystis jirovecii pneumonia, cytomegalovirus, progressive multifocal leukoencephalopathy, Epstein-Barr virus reactivation, and fungal pneumonias have been reported in patients receiving BTK inhibitors. The mechanism of this adverse event has been most well-described with ibrutinib. Infectious complications with ibrutinib may occur from mechanisms such as off-target interleukin-2-inducible T-cell kinase inhibition that impairs immune function, inhibition of natural killer cell antibody-dependent cellular cytotoxicity, or reduced macrophage phagocytosis (Borge et al., 2015; Dubovsky et al., 2013; Kohrt et al., 2014).

A recent meta-analysis reported an increased risk of both all-grade and grade 3 to 5 infectious complications in patients with B-cell malignancies taking ibrutinib compared with controls in randomized, controlled trials (Ball et al., 2020). Despite this risk, there are currently no standard guidelines or recommendations for routine antimicrobial prophylaxis in patients receiving BTK inhibitors. Immunocompromised patients or patients on long-term corticosteroids are at an increased risk for opportunistic infections such as Pneumocystis pneumonia and may benefit from anti-Pneumocystis prophylaxis while receiving BTK inhibitor therapy. Additionally, patients at an increased risk of infections taking zanubrutinib may also be considered for herpes simplex virus prophylaxis (BeiGene USA Inc., 2019).

Patients receiving a BTK inhibitor should be monitored for infectious complications throughout treatment. In the event of a serious grade 3 or 4 infectious complication, temporarily holding BTK inhibitor therapy should be considered until resolution of the infection.

**Dermatologic Toxicity**
Cutaneous adverse events have been reported with the BTK inhibitors and has been best described with ibrutinib (Iberri et al., 2016). Rash with ibrutinib is most likely to occur due to some of the off-target effects specific to ibrutinib, as it can also inhibit epidermal growth factor receptor
(EGFR), which is located in the skin. There are two distinct types of rashes with ibrutinib: a non-palpable, asymptomatic petechial rash and a palpable, eruptive rash with pruritic papules that can mimic leukocytoclastic vasculitis. Management of dermatologic toxicity with BTK inhibitors should be dependent on the severity, extent, and characteristics of the rash. Mild-to-moderate rashes can likely be managed with topical antihistamines and corticosteroids. Severe and extensive rashes may require oral antihistamines, systemic corticosteroids, and BTK inhibitor therapy interruption or dose reductions.

**Headaches**

Headaches are one of the most common adverse events associated with acalabrutinib, occurring in up to 40% of patients (AstraZeneca Pharmaceuticals LP, 2019). Most instances of headaches with acalabrutinib will be low grade; severe headaches do not occur commonly (~1%). Acalabrutinib-induced headaches are typically self-limiting and will resolve within the first 1 to 2 months of therapy. Patients can be offered supportive care with acetaminophen and caffeine supplements. Nonsteroidal anti-inflammatory drugs should be avoided due to the potential for increased risk of bleeding.

**Drug-Drug Interactions**

Ibrutinib, acalabrutinib, and zanubrutinib are all cytochrome P450 (CYP) 3A substrates and are all subject to drug-drug interactions with CYP3A inhibitors and inducers. This is especially important if atrial fibrillation is to occur, as some rate-control agents, specifically diltiazem and verapamil, are moderate CYP3A inhibitors and concomitant use will warrant a dose reduction of the BTK inhibitor. Recommendations for dose adjustments and management of drug-drug interactions with BTK inhibitors are described in Table 2.

Acalabrutinib also requires an acidic gastric environment for proper solubility. As the gastric

| Table 2. Drug-Drug Interactions With BTK Inhibitors |
|----------------------------------------------------|
| **Concomitant drug** | **Recommended mitigation strategy** |
| Ibrutinib | Moderate CYP3A inhibitors | Decrease ibrutinib to 280 mg once daily. |
| | Voriconazole 200 mg twice daily | Decrease ibrutinib to 140 mg once daily. |
| | Posaconazole suspension 100–400 mg daily | Decrease ibrutinib to 70 mg once daily. |
| | Posaconazole suspension 600–800 mg daily | Avoid concomitant use. Interrupt ibrutinib with short-term therapy (≤ 7 days). |
| | Posaconazole IV 300 mg once daily | Avoid concomitant use. |
| | Posaconazole DR tablets 300 mg daily | Avoid concomitant use. |
| | Other strong CYP3A inhibitors | Avoid concomitant use. |
| | Strong CYP3A inducers | Avoid concomitant use. |
| Acalabrutinib | Strong CYP3A inhibitor | Decrease acalabrutinib to 100 mg once daily. |
| | Strong CYP3A inducer | Avoid concomitant use. Interrupt acalabrutinib with short-term therapy (≤ 7 days). |
| | Proton pump inhibitor | Avoid concomitant use. If unable to avoid combination, increase acalabrutinib to 200 mg twice daily. |
| | Histamine-2 receptor antagonist | Take acalabrutinib 2 hours before taking histamine-2 receptor antagonist. |
| | Antacid | Separate dosing of acalabrutinib and antacids by at least 2 hours. |
| Zanubrutinib | Moderate CYP3A inhibitors | Decrease zanubrutinib to 80 mg twice daily. |
| | Strong CYP3A inhibitors | Decrease zanubrutinib to 80 mg once daily. |
| | Moderate and strong CYP3A inducers | Avoid concomitant use. |

**Note.** CYP = cytochrome P450; DR = delayed-release.
pH increases, the solubility of acalabrutinib decreases. Co-administration with a proton pump inhibitor has been shown to decrease the area under the curve of acalabrutinib by approximately 43%. It is recommended to avoid concomitant administration of proton pump inhibitors with acalabrutinib. Patients should take acalabrutinib 2 hours before taking histamine-2 receptor antagonists. Antacids and acalabrutinib administrations should be spaced out by at least 2 hours from each other.

CONCLUSION
The BTK inhibitors represent an important class of medications that have added significantly to the armamentarium of therapeutic agents available to treat several different types of B-cell malignancies. Patients receiving BTK inhibitors will be taking these medications until disease progression or intolerable toxicity, so there is a potential that patients will be on treatment for a prolonged duration of time. It is important that advanced practitioners treating patients with BTK inhibitors be familiar with their safety profiles, manage adverse events accordingly, manage drug-drug interactions appropriately, and assist patients with adherence so that therapy can be optimized for patients to achieve the best therapeutic outcomes for their B-cell malignancy.

Disclosure
The authors have no conflicts of interest to disclose.

References
AstraZeneca Pharmaceuticals LP. (2019). Calquence (acalabrutinib) package insert. https://www.azpicanet.com/calquence/calquence.pdf#page=1

Ball, S., Das, A., Vutthikraivit, W., Edwards, P. J., Hardwicke, F., Short, N. J.,…Mäit, A. (2020). Risk of infection associated with ibrutinib in patients with B-cell malignancies: A systematic review and meta-analysis of randomised controlled trials. Clinical Lymphoma Myeloma and Leukemia, 20(2), 87-97.e5. https://doi.org/10.1016/j.clml.2019.10.004

BeiGene USA Inc. (2019). Brukinsa (zanubrutinib) package insert. https://www.brukinsa.com/prescribing-information.pdf

Borge, M., Almeijun, M. B., Podaza, E., Colado, A., Grecco, H. F., Cabrejo, M.,…Gamberale, R. (2015). Ibrutinib impairs the phagocytosis of rituximab-coated leukemic cells from chronic lymphocytic leukemia patients by human macrophages. Haematologica, 100(4), e140–e142. https://doi.org/10.3324/haematol.2014.119669

Buggy, J. J., & Elias, L. (2012). Bruton tyrosine kinase (BTK) and its role in B-cell malignancy. International Reviews of Immunology, 31(2), 119–132. https://doi.org/10.1080/08830185.2012.664797

Burger, J. A., Barr, P. M., Robak, T., Owen, C., Ghia, P., Tedeschi, A.,…Kipps, T. J. (2020). Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia, 34(3), 787–796. https://doi.org/10.1038/s41375-019-0602-x

Byrd, J. C., Brown, J. R., O’Brien, S., Barrientos, J. C., Kay, N. E., Reddy, N. M.,…Delgado, J. (2014). Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. New England Journal of Medicine, 371(3), 213–223. https://doi.org/10.1056/nejmoa1400376

Coutre, S. E., Byrd, J. C., Hillmen, P., Barrientos, J. C., Barr, P. M., Devereux, S.,…O’Brien, S. M. (2019). Long-term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies. Blood Advances, 3(12), 1799–1807. https://doi.org/10.1182/bloodadvances.2018028761

Dickerson, T., Wiczer, T., Waller, A., Philippin, J., Porter, K., Haddad, D.,…Addison, D. (2019). Hypertension and incident cardiovascular events following ibrutinib initiation. Blood, 134(22), 1919–1928. https://doi.org/10.1182/blood.2019000840

Dimopoulos, M. A., Tedeschi, A., Trotman, J., Garcia-Sanz, R., Macdonald, D., Leblond, V.,…Buske, C. (2018). Phase 3 trial of ibrutinib plus rituximab in Waldenström’s macroglobulinemia. New England Journal of Medicine, 378(25), 2399–2410. https://doi.org/10.1056/nejmoa1802917

Dubovsky, J. A., Beckwith, K. A., Natarajan, G., Woyach, J. A., Jaglowski, S., Zhong, Y.,…Lehman, A. M. (2013). Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. Blood, 122(15), 2539–2549. https://doi.org/10.1182/blood-2013-06-507947

Ghia P, Pluta A, Wach M, Lysak, D, Kozak, T, Simkovic,...Jurczak W (2019). ASCEND phase 3 study of acalabrutinib vs investigator’s choice of rituximab plus idelalisib (IDR) or bendamustine (BR) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). HemaSphere, 3(1), 36–44. https://doi.org/10.1016/j.hema.2019.06.003

Iberri, D. J., Kwong, B. Y., Stevens, L. A., Coutre, S. E., Kim, J., Sabile, J. M.,…Kipps, T. J. (2020). Long-term efficacy and safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia. International Reviews of Immunology, 39(2), 119–132. https://doi.org/10.3109/08830185.2019.1680030

J Adv Pract Oncol 446 AdvancedPractitioner.com

Liu, J., Fitzgerald, M. E., Berndt, M. C., Jackson, C. W., & Gartner, T. K. (2006). Bruton tyrosine kinase is essential for botrocetin/VWF-induced signaling and GPIb-dependent thrombus formation in vivo. Blood, 108(8), 2596–2603. https://doi.org/10.1182/blood-2006-01-011817

Moreno, C., Greil, R., Demirkan, F., Tedeschi, A., Anz, B.,...
Larratt, L., Flinn, I. W. (2019). Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iL-LUMINATE): A multicentre, randomised, open-label, phase 3 trial. *Lancet Oncology*, 20(1), 43–56. https://doi.org/10.1016/s1470-2045(18)30788-5

Munir, T., Brown, J. R., O’Brien, S., Barrientos, J. C., Barr, P. M., Reddy, N. M., Woyach, J. A. (2019). Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *American Journal of Hematology*, 94(12), 1353–1363. https://doi.org/10.1002/ajh.25638

Noy, A., de Vos, S., Thieblemont, C., Martin, P., Flowers, C. R., Morschhauser, F., Chen, R. (2017). Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. *Blood*, 129(16), 2224–2232. https://doi.org/10.1182/blood-2016-10-747345

Pharmacyclics. (2018). Imbruvica (ibrutinib) package insert. https://imbruvica.com/files/prescribing-information.pdf

Rule, S., Jurczak, W., Jerkeman, M., Rusconi, C., Trneny, M., Offner, F., Dreyling, M. (2018). Ibrutinib versus temsirolimus: 3-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study. *Leukemia*, 32(8), 1799–1803. https://doi.org/10.1038/s41375-018-0023-2

Shanafelt, T. D., Wang, X. V., Kay, N. E., Hanson, C. A., O’Brien, S., Barrientos, J., Litzow, M. (2019). Ibrutinib–rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *New England Journal of Medicine*, 381(5), 432–443. https://doi.org/10.1056/nejmoa1817073

Sharman, J. P., Egyed, M., Jurczak, W., Skarbnik, A., Pagel, J. M., Flinn, I. W., Cymbalista, F. (2020). Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE-TN): A randomised, controlled, phase 3 trial. *Lancet*, 395(10232), 1278–1291. https://doi.org/10.1016/s0140-6736(20)30262-2

Song, Y., Zhou, K., Zou, D., Zhou, J., Hu, J., Yang, H., Han, L. (2019). Zanubrutinib in patients with relapsed/refractory mantle cell lymphoma [Abstract no. 015]. *Hematological Oncology*, 37(S2), 45–46. https://doi.org/10.1002/hon.15.2629

Stephens, D. M., & Byrd, J. C. (2019). How I manage ibrutinib intolerance and complications in patients with chronic lymphocytic leukemia. *Blood*, 133(12), 1298–1307. https://doi.org/10.1182/blood-2018-11-846808

Wang, M., Rule, S., Zinzani, P. L., Goy, A., Casasnovas, O., Smith, S. D., Robak, T. (2018). Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): A single-arm, multicentre, phase 2 trial. *Lancet*, 391(10121), 659–667. https://doi.org/10.1016/s0140-6736(17)33108-2

Wang, M. L., Rule, S., Martin, P., Goy, A., Auer, R., Kahl, B. S., Zhang, L. (2013). Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *New England Journal of Medicine*, 369(6), 507–516. https://doi.org/10.1056/nejmoa1306220

Woyach, J. A., Ruppert, A. S., Heerema, N. A., Zhao, W., Booth, A. M., Ding, W., Nattam, S. (2018). Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *New England Journal of Medicine*, 379(26), 2517–2528. https://doi.org/10.1056/nejmoa1812836