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PRODUCT PERSPECTIVES

Brukinsa® (Zanubrutinib) for Chronic Lymphocytic Leukemia

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What is the clinical impact of chronic lymphocytic leukemia (CLL)?

Chronic lymphocytic leukemia (CLL) is an incurable condition. Once diagnosed, CLL persists for the entirety of the patient's life and can be associated with symptoms such as lymphadenopathy, blood count abnormalities, and an increased risk of infections. Patients often report fatigue.[1] Many patients ultimately require treatment, which historically has consisted of chemoimmunotherapy regimens. However, over the last decade, we have moved toward increased use of novel targeted therapies such as Bruton's tyrosine kinase (BTK) inhibitors, B-cell leukemia/lymphoma 2 protein (BCL-2) inhibitors, and/or second-generation anti-CD20 antibodies.[2]

Most patients with CLL will be able to maintain control of their disease and enjoy normal, or close to normal, lifespans.[1] Patients diagnosed at a younger age will need treatment options that provide disease control for a long time, which may present challenges. There is also a subset of high-risk patients with a 17p deletion or TP53 mutations who are more resistant to therapy, and may not experience the same duration of benefit from therapeutic options as their counterparts who lack these abnormalities. For these high-risk patients, the duration of treatment benefits tends to get progressively shorter with each successive regimen. They cycle through treatment options more rapidly as they develop resistance, and may ultimately have shorter lifespans due to these genetic abnormalities.

What treatments are available for CLL?

We have evolved from the traditional chemoimmunotherapy regimens to the use of very effective targeted agents, primarily BTK inhibitors such as ibrutinib, acalabrutinib, and zanubrutinib; the BCL-2 inhibitor venetoclax; and novel anti-CD20 antibodies such as obinutuzumab.[2] For most patients, frontline treatment options will consist of either BTK therapy, or the combination of obinutuzumab plus venetoclax. For patients with relapsed disease, switching drug classes is often logical, although there are some relapsed patients for whom re-treatment may make sense. For instance, a patient might be switched from one BTK agent to another if the original agent was discontinued for reasons other than disease progression, or obinutuzumab with venetoclax might be reused for patients who received a durable benefit from their initial therapy with this combination.[2]

BTK inhibitors are administered continuously for an indefinite period, whereas obinutuzumab plus venetoclax is a fixed-duration course that typically lasts a year as a frontline treatment, or 2 years with relapsed/

refractory (R/R) CLL. Because BTK inhibitors are not a fixed-duration therapy, minimizing side effects with these agents during long-term therapy is important. To that end, recent updates to the National Comprehensive Cancer Network® (NCCN®) guidelines for CLL/small lymphocytic lymphoma (SLL) B-cell lymphomas now recommends acalabrutinib and zanubrutinib ahead of the first-generation BTK inhibitor ibrutinib, which has higher rates of side effects.[2] It is important that we make sure patients with CLL get an effective BTK inhibitor and that treatment is not limited by side effects.

Specifically, what is the role of Bruton's tyrosine kinase in CLL?

In CLL, B-cell receptor signaling helps drive the proliferation and survival of malignant lymphocytes. This signaling cascade is promoted by a series of kinases, including spleen tyrosine kinase (SYK), BTK, and phosphoinositide 3-kinases (PI3K). Inhibition of BTK interrupts this signaling cascade.[3]

BTK inhibitors are one of the most important therapeutic classes available to us right now, and this medication is given continuously from the time the condition is diagnosed until its progression. BTK inhibitors are useful in both previously untreated patients, as well as in patients with R/R disease. Ibrutinib, acalabrutinib, and zanubrutinib are now approved in this setting for the treatment of CLL.

These agents are typically able to control a patient's disease for multiple years, and patients can do so with relatively modest side effects from therapy, including increased bruising or bleeding, and a potentially increased risk of hypertension. First-generation BTK inhibitors may result in increased rates of atrial fibrillation, which seems to be reduced in frequency among the second-generation BTK inhibitors acalabrutinib and zanubrutinib.[3]

What challenges does BTK inhibition present?

Drugs very rarely exclusively inhibit the target they were designed to inhibit, and this is the case with BTK inhibitors. Off-target activity of BTK inhibitors may result in cytopenias or cardiac abnormalities such as hypertension, atrial fibrillation, and potentially cardiac tachyarrhythmias,[4,5] although the mechanism driving the cardiac events is unclear. Not all adverse effects are off-target. For example, we see patients with an increased risk of bruising,[4,5] which may result from an on-target BTK inhibitor effect in platelets. Any of these side effects can be an issue during long-term use of first- or second-generation BTK inhibitors.

With the first-generation BTK inhibitor ibrutinib, off-target effects such as Interleukin-2-Inducible T-Cell Kinase (ITK) or epidermal growth factor receptor (EGFR) inhibition can adversely impact its tolerability/efficacy ratio. ITK is the T-cell equivalent of BTK, and its inhibition may diminish immune function within the T-cell compartment. We do see a slightly increased rate of invasive fungal infections.[4,5] EGFR inhibition can lead to a rash—which is fairly uncommon—but, fingernail fragility and paronychia may evolve, particularly during long-term therapy. These effects aren't necessarily dangerous, but they can be bothersome and cause discomfort.

Maintaining BTK occupancy is also an issue with these agents. Both first-generation (ibrutinib) and second-generation (acalabrutinib and zanubrutinib) BTK inhibitors covalently modify the BTK enzyme. Taken orally, these drugs get into the serum and bind to the BTK enzyme, leading to complete BTK inhibition. However, BTK resynthesis typically occurs beginning within ~24 hours of administration. Since BTK inhibitors have a relatively short half-life, you need repeated exposure to maintain BTK inhibition, and some may provide better target coverage than others.

How is zanubrutinib a unique compound?

Zanubrutinib has a longer half-life than acalabrutinib and is the most selective of the first- or second-generation BTK inhibitors, meaning zanubrutinib maintains high levels of BTK inhibition with fewer untoward off-target effects.[6,7] As a result, zanubrutinib might be an option for patients who are intolerant to either ibrutinib or acalabrutinib. We've seen literature indicate that when patients are intolerant of one BTK inhibitor, they can frequently transition to another BTK inhibitor.

Accordingly, acalabrutinib or zanubrutinib are often tolerated by patients with intolerance to an alternative BTK inhibitor. In a small phase 2 study (n=17; 12 with CLL/SLL), 11 patients (65%) who were intolerant of acalabrutinib tolerated zanubrutinib. Seven of 21 intolerance events occurring in 6 patients recurred on zanubrutinib, and 2 patients discontinued due to recurrence. Among 14 efficacy-evaluable patients, 13 (93%) achieved stable disease on zanubrutinib and 9 (64%) had a deepening response.[6] The longer half-life also means zanubrutinib can be given once daily as 4 capsules taken all at once, or twice daily if the patient prefers.[4] In contrast, acalabrutinib is given twice daily.[5]

Can you discuss the phase 3 ALPINE Trial that supported the approval of zanubrutinib in CLL?

Published in January 2023, the phase 3 ALPINE trial compared

zanubrutinib and ibrutinib in patients with CLL who had R/R CLL after at least one prior line of treatment.[8] The primary outcome was the overall response rate (ORR), which included both complete response (CR) and partial response (PR), but excluded PR with lymphocytosis (PR-L), as per the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines.[8] After a median follow-up of 24 months, zanubrutinib showed a significantly higher ORR (79.5% vs 71.1%; P=0.0133). As in the total population, the ORR was higher with zanubrutinib vs ibrutinib in subgroups with del(17p)/TP53 mutations (81.3% vs 64.0%).[8] At 24 months, the progression-free survival rate was higher with zanubrutinib than with ibrutinib (78.4% vs 65.9%), which represents a 35% relative risk reduction (hazard ratio, 0.65; 95% confidence interval, 0.49-0.86; P=0.002).[9]

Rates of atrial fibrillation or flutter were lower with zanubrutinib vs ibrutinib (5.2% vs 13.3%).[8] Rates of cardiac events, major hemorrhages, and adverse events leading to treatment discontinuation/death were lower with zanubrutinib. Collectively, these results support the idea that more complete, sustained BTK occupancy may improve efficacy, while more specific binding, with fewer off-target effects, may improve tolerability.

It is unclear whether these pharmacologic differences might distinguish zanubrutinib from acalabrutinib, as we have not seen a head-to-head comparison of the two second-generation BTK inhibitors. However, while both second-generation BTK inhibitors have shown superior safety vs ibrutinib, only zanubrutinib showed superior efficacy vs ibrutinib.[8,9]

What are the NCCN® guideline recommendations for the use of BTK inhibitors?

We have recently seen that the NCCN® has listed both acalabrutinib and zanubrutinib as preferred BTK agents, with ibrutinib being moved to additional regimens that may be suitable.[2] The NCCN® is probably considering trials comparing the second-generation BTK inhibitors with first-generation ibrutinib in which the side effect profile for zanubrutinib and acalabrutinib appeared to be more favorable vs ibrutinib.[8,9]

From an efficacy perspective, it cannot be determined whether there is an advantage of zanubrutinib over acalabrutinib. It is tempting to make indirect comparisons between these agents because the pivotal studies of each used the same control arm.[8,9] However, the studies were conducted at different times, in different subsets of patients, and in different clinical landscapes. Moreover, there were significant differences in between the performance of the control arm between the studies.[8,9] A head-to-head comparison of zanubrutinib and acalabrutinib would be needed to allow for firm conclusions.

How does zanubrutinib compare to other approved BTK inhibitors in terms of value and economic impact?

The wholesale prices for a 30-day supply of available BTK inhibitors are $13 997 for zanubrutinib, $14 486 for acalabrutinib, and $16 024* for ibrutinib tablets. This represents a cost reduction of $489 with zanubrutinib (3.5%) vs acalabrutinib and $2027 (14.5%) vs ibrutinib tablets.[10]

Generally, the impact of BTK inhibitors—and zanubrutinib in particular—on overall costs has not been formally studied; however, it might be hypothesized that improved tolerability with the second-generation BTK inhibitors may reduce treatment costs. In a 2021 study, monthly costs associated with ibrutinib adverse events were $2473 for anemia, $1281 for atrial fibrillation, $631 for bleeding, $2232 for infection, and $1412 for pneumonia.[11] In the ALPINE trial, rates of atrial fibrillation were significantly lower with zanubrutinib vs ibrutinib.[8] Rates of major bleeding and cardiac events were also lower. With fewer off-target effects, zanubrutinib and other next-generation BTK inhibitors may offer cost savings vs ibrutinib beyond differences in acquisition cost. However, this remains to be examined in head-to-head cost comparisons.

* Ibrutinib is dispensed as 28 tablets. The price here is converted up to a 30-day supply.

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PRODUCT MONOGRAPH

Brukinsa® zanubrutinib

INDICATION

BRUKINSA® is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage

Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA® monotherapy. Grade 3 or higher hemorrhage, including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 3.6% of patients treated with BRUKINSA® monotherapy in clinical trials, with fatalities occurring in 0.3% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 30% of patients.

Bleeding has occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Coadministration of BRUKINSA® with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA® if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA® for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

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PRODUCT INFORMATION

BRUKINSA® (zanubrutinib) is a small-molecule Bruton's tyrosine kinase (BTK) inhibitor indicated for the treatment of adult patients with CLL and SLL. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signaling results in the activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. As a small-molecule BTK inhibitor, BRUKINSA® forms a covalent bond with cysteine residue in the BTK active site, leading to the inhibition of BTK activity. In nonclinical studies, BRUKINSA® inhibited malignant B-cell proliferation and reduced tumor growth.

IMPORTANT SAFETY INFORMATION

WARNINGS & PRECAUTIONS, CONTINUED

Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA® monotherapy. Grade 3 or higher infections occurred in 24% of patients, most commonly pneumonia (11%), with fatal infections occurring in 2.9% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

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Table 1. Efficacy Data in SEQUOIA (patients without the del(17p) mutation)

	BRUKINSA® (n=241)	BR (n=238)
PFS, number of events (%)	36 (15)*	71 (30)
Disease Progression	27 (11)	59 (25)
Deaths	9 (3.7)	12 (5)
Median PFS, Months (95% CI)	NE (NE, NE)	33.7 (28.1, NE)
Hazard Ratio (95% CI)	0.42 (0.28, 0.63)*	
ORR, number of events (%)**	225 (93)	203 (85)
95% CI	89, 96	80, 90

BR= bendamustine/rituximab; ORR= overall response rate; PFS= progression-free survival.
*Hazard Ratio P<0.0001 vs BR reference regiment.
**ORR included patients with complete response (CR), complete response with incomplete hematopoietic recovery (CRi), partial response (PR), and nodular partial response (nPR). No patient had CRi as best response.

PHARMACODYNAMICS/ PHARMACOKINETICS

In patients with B-cell malignancies treated with BRUKINSA® 320 mg/day, the median steady-state BTK occupancy in peripheral blood mononuclear cells was maintained at 100% over a 24-hour period. The median steady-state BTK occupancy in lymph nodes was maintained at 94% to 100% over 24 hours following administration of the approved recommended BRUKINSA® doses (160 mg twice daily or 320 mg once daily), with no clinically relevant effects on the corrected QT (QTc) interval. The effect of BRUKINSA® on the QTc interval above the therapeutic exposure has not been evaluated.

The BRUKINSA® maximum plasma concentration (C_{max}) and area under the plasma drug concentration over time curve (AUC) increases proportionally over a dosage range from 40 mg to 320 mg (0.13 to 1 time the recommended total daily dose). Limited systemic accumulation of BRUKINSA® was observed following repeated administration.

The geometric mean (%CV) zanubrutinib steady-state daily AUC is 2099 (42%) ng·h/mL, following 160 mg twice daily and 1917 (59%) ng·h/mL, following 320 mg once daily. The geometric mean (%CV) zanubrutinib steady-state C_{max} is 295 (55%) ng/mL, following 160 mg twice daily, and 537 (55%) ng/mL following 320 mg once daily. The median time to reach C_{max} (t_{max}) of zanubrutinib is 2 hours, and the mean half-life ($t_{½}$) is approximately 2- to 4- hours following a single 160 mg or 320 mg oral. Zanubrutinib is primarily metabolized by cytochrome P450 (CYP) 3A.

In healthy subjects, no clinically significant differences in zanubrutinib AUC or C_{max} were observed following administration of a high-fat meal comprised of ~1,000 calories, of which 50% of the caloric content was from fat. No clinically significant differences in zanubrutinib pharmacokinetics were observed when co-administered with gastric acid-reducing agents (proton pump inhibitors, H2-receptor antagonists).

No clinically significant differences in the pharmacokinetics of zanubrutinib were observed based on age (19- to 90-years), sex, race (Asian, Caucasian, and Other), body weight (36- to 144-kg) or mild, moderate, or severe renal impairment (creatinine clearance [CLcr] ≥ 15 mL/min as estimated by Cockcroft-Gault). The effect of dialysis on zanubrutinib pharmacokinetics is unknown.

CLINICAL TRIAL DATA

Efficacy

The efficacy of BRUKINSA® in patients with CLL/SLL was evaluated in two randomized, multicenter, open-label, actively controlled phase 3 trials enrolling previously untreated patients with CLL/SLL (the SEQUOIA trial;NCT0333633) and patients

IMPORTANT SAFETY INFORMATION

WARNINGS & PRECAUTIONS, CONTINUED

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (22%), thrombocytopenia (8%) and anemia (7%) based on laboratory measurements, developed in patients treated with BRUKINSA® monotherapy. Grade 4 neutropenia occurred in 11% of patients, and Grade 4 thrombocytopenia occurred in 2.8% of patients.

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with relapsed/refractory (R/R) disease (the ALPINE trial; NCT03734016).

Previously-Untreated Patients: SEQUOIA

In the SEQUOIA trial, 479 previously untreated adult patients with CLL/SLL, without the 17p deletion (del(17p)) mutation, received BRUKINSA® 160 mg/bid until disease progression or unacceptable tolerability, or a standard regimen of bendamustine/rituximab (BR) given in 6 cycles of ~28 days each. The efficacy of BRUKINSA® monotherapy was also examined in a separate single-arm study of 110 patients with previously untreated CLL/SLL, but with centrally confirmed del(17p) mutation.

Progression-free survival (PFS) were determined by an independent central review committee (IRC) using International Workshop for Chronic Lymphocytic Leukemia (iWCLL) guidelines for CLL, and the Lugano criteria for SLL. The overall response rate (ORR) was calculated as the sum of patients with complete response (CR), complete response with incomplete hematopoietic recovery (CRi), partial response (PR), and nodular partial response (nPR).

In patients without the del(17p) mutation, baseline demographics and disease characteristics were similar between treatment arms. The median age was 70 years; 62% were male; and 89% were white, 3% were Asian, and 1% were Black. Fifty-three percent of patients had an unmutated immunoglobulin heavy chain gene (*IGHV*) and 29% had Binet stage C disease. The estimated median duration of follow-up for PFS was 25 months. The event-free rate was 85% for BRUKINSA® and 70% for BR. Median PFS was 33.7 months in the BR group, but was not reached in the BRUKINSA® group. The ORR with BRUKINSA® was 93%, compared with 85% for BR (**Table 1**).

At the time of this analysis, overall survival data was immature. During an estimated median follow-up of 25.7 months, median overall survival was not reached in either treatment arm. Fewer than 7% of patients experienced an event.

In the cohort of patients with del(17p) mutation, the median age was 70 years. Seventy-one percent were male, 95% were White, and 1% were Asian. Sixty percent of patients had an unmutated *IGHV* gene and 35% had Binet stage C disease.

As shown in **Table 2**, the ORR in patients with a del(17p) mutation was nearly as high as in patients without the mutation (88%). Response was generally rapid and durable. During an estimated median follow-up of 25.1 months, median duration of response (DOR) was not reached. The estimated median follow-up for duration of response was 25.1 months.

Table 2. Efficacy Data in SEQUOIA (patients with the del(17p) mutation)

	Patients (n=110)
Response, n(%)	
ORR*	97 (88)
CR	7 (6)
nPR	2 (1.8)
PR	88 (80)
Time to response, months	
Median	2.9
Range	1.9-13.9
Median DOR (95% CI), months**	NE (NE, NE)
Range, months	5.6-35.9
Response rate at 12 months, % (95% CI)	96 (89, 98)
Response rate at 18 months, % (95% CI)	95 (88, 98)

CR= complete response; CRi= complete response with incomplete hematopoietic recovery; DOR= duration of response; ORR= overall response rate; PR= partial response; nPR= nodular partial response.
*ORR included patients with CR, CRi, PR, and nPR. No patient had CRi as best response.
**Median follow-up 25.1 months

Relapsed/Refractory Patients: ALPINE

In ALPINE, 652 patients with relapsed or refractory CLL/SLL and ≥1 prior systemic therapy received BRUKINSA® 160 mg orally twice daily (n=327) or ibrutinib 420 mg orally once daily (n=325) until disease progression or unacceptable toxicity. The primary efficacy endpoint was the ORR (defined as in SEQUOIA), determined by an IRC using iWCLL guidelines for CLL and the Lugano criteria for SLL.

IMPORTANT SAFETY INFORMATION

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted. Treat using growth factor or transfusions, as needed.

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Table 3. Efficacy Data in ALPINE

	Zanubrutinib (n=327)		Ibrutinib (n=325)
Response, n(%)			
ORR*	263 (80)		237 (73)
CR	13 (4.0)		8 (2.5)
nPR	1 (0.3)		0
PR	249 (76)		229 (70)
Response rate ratio (95% CI		1.10 (1.01, 1.20)	
2-sided p-value		0.0264	
Time to response, months			
Median	5.5		5.6
Range	2.6-22.1		2.3-19.8
Median DOR (95% CI), months**	NE (NE, NE)		NE (NE, NE)
Range, months	1.4-30.4+		1.9-30.8+
Response rate at 12 months, % (95% CI)	96 (89, 98)		86 (80, 91)

ORR= overall response rate; CR=complete response; CRi=complete response with incomplete hematopoietic recovery; DOR=duration of response; PR=partial response; nPR=nodular partial response
*ORR included patients with CR, CRi, PR, and nPR. No patient had CRi as best response.
**Median follow-up 14.1 months

Baseline characteristics were similar between treatment arms. Overall, the median patient age was 67 years. Sixty-eight percent of patients were male, 81% were White, 14% were Asian, and 1% were Black. Forty-three percent had advanced stage disease, 73% had an unmutated *IGHV* gene, and 23% had del(17p) or TP53 mutation. Patients had received a median of one prior line of therapy (range: 1-8). Eighteen percent of patients had ≥3 prior lines of therapy, 78% had prior chemoimmunotherapy, and 2.3% had previously received a B-cell leukemia/lymphoma 2 protein (BCL-2) inhibitor.

The ORR was 80% for BRUKINSA® and 73% for ibrutinib (**Table 3**). Median DOR was not reached during 14.1 months of follow-up, but 92% of patients in the BRUKINSA® group, compared with 86% in the ibrutinib group, had sustained response at 12 months. At the time of this analysis, overall survival data were immature. During an estimated median follow-up of 24.7 months, median overall survival was not reached in either arm. Eleven percent of patients experienced an event.

Safety

The safety of BRUKINSA® was evaluated in a total of 675 patients with CLL/SLL enrolled in SEQUOIA (n=391) or ALPINE (n=324).

SEQUOIA

In SEQUOIA, BRUKINSA® was administered to 240 previously-untreated patients with CLL/SLL without del(17p) mutations, and another 111 previously-untreated patients with del(17p) mutations. The median duration of BRUKINSA® exposure was 26 months in patients without a del(17p) mutation, and 30 months in patients with a del(17p) mutation.

In patients without del(17p) mutation, adverse reactions leading to death occurred in 11 (4.6%) patients, most commonly due to COVID-19 infection (2.1%). Eighty-seven patients (36%) reported ≥1 serious adverse reactions, the most frequent of which were pneumonia and a second primary malignancy (5% each). Adverse reactions led to treatment discontinuation in 8% of patients, dose reduction in 8%, and dose interruption in 46%. The most common adverse reactions leading to permanent discontinuation were second primary malignancy and COVID-19. The leading causes of dose modification (≥5% of all patients) were respiratory

IMPORTANT SAFETY INFORMATION

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 13% of patients treated with BRUKINSA® monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 7% of patients. Other second primary malignancies included malignant solid tumors (5%), melanoma (1.2%), and hematologic malignancies (0.5%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

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infections (COVID-19, pneumonia) and hemorrhage. Other clinically significant adverse reactions occurring in <10% of BRUKINSA® recipients in this cohort included COVID-19 (9%), edema (8%), abdominal pain (8%), urinary tract infection (7%), and atrial fibrillation or flutter (3.3%).

In patients with del(17p) mutations, adverse reactions leading to death occurred in 3 (2.7%) patients. The causes of death were pneumonia (0.9%), renal insufficiency (0.9%), and aortic dissection in the same patient (0.9%). Serious adverse reactions occurred in 41% of patients. The most frequent serious adverse reactions were pneumonia (8%) and a second primary malignancy (7%). Five percent of patients discontinued due to adverse reactions, 5% required a dose reduction, and dose interruptions were necessary for 51%. The most frequent reasons for dose modifications (≥5% of patients) were pneumonia, neutropenia, second primary malignancy, and diarrhea.

Clinically significant adverse reactions occurring in <10% of BRUKINSA® recipients in this cohort included urinary tract infection (8%), edema (7%), atrial fibrillation or flutter (4.5%), and COVID-19 (3.6%).

Table 4. Adverse Reactions Occurring in ≥10% of Patients With CLL/SLL in ALPINE (Intent-to-Treat Population)

Body System	Adverse Reaction	Patients Treated With BRUKINSA® (n=324)	
		All Grades %	Grade ≥3, %
Gastrointestinal disorders	Diarrhea	14	1.5
General disorders	Fatigue	13	0.9
Hematologic abnormalities	Neutropenia	43	15
	Hemoglobin decreased	28	4
	Lymphocytosis	24	19
	Thrombocytopenia	22	4
Infections and infestations	Upper respiratory tract infection	27	1.2
	Pneumonia	18	9
	COVID-19	14	7
Musculoskeletal & connective tissue disorders	Musculoskeletal pain	26	0.6
Nervous system disorders	Dizziness	10	0
Respiratory, thoracic and mediastinal disorders	Cough	11	0.3
Skin and subcutaneous tissue disorders	Rash	20	1.2
	Bruising	16	0
Vascular disorders	Hemorrhage	24	2.5
	Hypertension	19	13

ALPINE

In ALPINE, safety was assessed in 324 patients with R/R CLL/SLL who received BRUKINSA® monotherapy and 324 patients who received ibrutinib monotherapy. Both treatments were administered until disease progression or unacceptable toxicity.The median duration of exposure was 24 months for BRUKINSA®.

Adverse reactions leading to death in the BRUKINSA® arm occurred in 24 (7%)patients. The most frequent fatal adverse reactions were pneumonia (2.8%) and COVID-19 infection (1.9%). No other fatal reaction occurred in ≥1% of patients.

One hundred and four patients in the BRUKINSA® arm (32%) experienced ≥1 serious adverse reaction. Serious adverse reactions occurring in ≥5% of patients were pneumonia (10%), COVID-19 (7%), and second primary malignancies (5%).

IMPORTANT SAFETY INFORMATION

WARNINGS & PRECAUTIONS, CONTINUED

Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA®. Atrial fibrillation and atrial flutter were reported in 3.7% of 1550 patients treated with BRUKINSA® monotherapy, including Grade 3 or higher cases in 1.7% of patients. Patients with cardiac risk factors, hypertension and acute infections may be at increased risk. Grade 3 or higher ventricular arrhythmias were reported in 0.2% of patients.

Monitor for signs and symptoms of cardiac arrhythmias (eg, palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately, and consider the risks and benefits of continued BRUKINSA® treatment.

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Table 5. Recommended Dose Modifications for Potential Drug-to-Drug Interactions and Adverse Reactions (Starting Dose, 160 mg/bid or 320 mg/QD)

Dose Modifications for BRUKINSA® With CYP3A4 Inhibitors/Inducers	
Co-administered Drug	**Recommended BRUKINSA® Dose**
Co-administered Drug	80 mg once daily
Strong CYP3A inhibitor	80 mg twice daily
Moderate CYP3A inhibitor	Avoid concomitant use
Strong CYP3A inducer	Avoid concomitant use (if these inducers cannot be
Moderate CYP3A inducer	avoided, increase BRUKINSA® dose to 320 mg/bid)

Dose Modifications for Adverse Reactions		
Adverse Reaction	**Reaction Occurrence**	**Dose Modification**
Grade 3 or 4 febrile neutropenia Platelet count decreased to 25,000=50,000/mm^3 with significant bleeding	First	Interrupt BRUKINSA® Once toxicity has resolved to Grade ≤1 or baseline, resume at 160 mg/bid or 320 mg/QD
Neutrophile decreased to <500/mm^3 (>10 consecutive days)	Second	Interrupt BRUKINSA® Once toxicity has resolved to Grade ≤1 or baseline, resume at 80 mg/bid or 160 mg/QD
Platelet count decreased to <25,000/mm^3 (>10 consecutive days)	Third	Interrupt BRUKINSA® Once toxicity has resolved to Grade ≤1 or baseline: Resume at 80/QD
Severe or life-threatening non-hematological toxicities	Fourth	Discontinue BRUKINSA®

Adverse reactions led to treatment discontinuation in 13% of patients, dose reduction in 11%, and dose interruption in 42%. The leading cause of treatment discontinuation was pneumonia. The leading causes of dose modification (≥5% of all patients) were respiratory infections (COVID-19, pneumonia) and neutropenia.

Adverse reactions occurring in ≥10% of patients are presented in **Table 4**. Clinically relevant adverse reactions in <10% of patients who received BRUKINSA® included urinary tract infection (9%), supraventricular arrhythmias (9%) including atrial fibrillation or flutter (4.6%), abdominal pain (8%), headache (8%), pruritus (6.2%), constipation (5.9%), and edema (4.6%).

IMPORTANT SAFETY INFORMATION

Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA® can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA®, and for 1 week after the last dose. Advise men to avoid fathering a child during treatment, and for 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Adverse Reactions

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in ≥30% of patients who received BRUKINSA® (N=1550) included decreased neutrophil count (42%), upper respiratory tract infection (39%), decreased platelet count (34%), hemorrhage (30%), and musculoskeletal pain (30%).

Please see full Prescribing Information after page 10

DOSAGE AND ADMINISTRATION

BRUKINSA® comes in 80-mg capsules packaged in a 120-count bottle. BRUKINSA® should be stored at 20 °C to 25 °C (68 °F to 77 °F). Excursions are permitted between 15 °C to 30 °C (59 °F to 86 °F). The recommended dosage of BRUKINSA® is 160 mg taken orally twice daily, or 320 mg taken orally once daily until disease progression or unacceptable toxicity.

BRUKINSA® capsules should be swallowed whole with water and can be taken with or without food. Patients should be advised not to open, break, or chew capsules. If a dose of BRUKINSA® is missed, it should be taken as soon as possible on the same day, with a return to the normal schedule the following day.

The recommended BRUKINSA® dose for patients with severe hepatic impairment is 80 mg orally twice daily. Dose modifications for use with CYP3A inhibitors or inducers, and for adverse reactions are presented in **Table 5**.

SUMMARY

BRUKINSA® is a second-generation BTK inhibitor with superior efficacy and safety compared with standard chemoimmunotherapy regimens (eg, bendamustine/rituximab) and the first-generation BTK inhibitor ibrutinib. In untreated patients with CLL/SLL, BRUKINSA® was significantly more effective than a 6-cycle regimen of bendamustine/rituximab. Similar efficacy was observed in patients with and without del(17p) mutations. In patients with R/R CLL/SLL, BRUKINSA® was significantly more effective than ibrutinib, regardless of del(17p) status, with a similar response judged both by investigators and a more neutral IRC. BRUKINSA® was also associated with superior cardiac safety vs ibrutinib. These clinical trial results suggest that BRUKINSA® represents an important new option for patients with CLL/SLL. Final ALPINE study results will further clarify the role of BRUKINSA® in this patient population.

IMPORTANT SAFETY INFORMATION

WARNINGS & PRECAUTIONS, CONTINUED

Drug Interactions

CYP3A Inhibitors: When BRUKINSA® is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA® dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA® dose to 80 mg twice daily.

CYP3A Inducers: Avoid coadministration with strong or moderate CYP3A inducers. Dose adjustment may be recommended with moderate CYP3A inducers.

SPECIFIC POPULATIONS

Lactations: Advise not to breastfeed.

Hepatic Impairment: The recommended dose of BRUKINSA® for patients with severe hepatic impairment is 80 mg orally twice daily.

INDICATIONS

• BRUKINSA® is a kinase inhibitor indicated for the treatment of adult patients with:

- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
- Waldenström's macroglobulinemia (WM)
- Mantle cell lymphoma (MCL) who have received at least one prior therapy
- Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen

The MCL and MZL indications are approved under accelerated approval based on the overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Please see full Prescribing Information after page 10

Brukinsa™
80 mg capsules
zanubrutinib

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BRUKINSA safely and effectively. See full prescribing information for BRUKINSA.

BRUKINSA® (zanubrutinib) capsules, for oral use
Initial U.S. Approval: 2019

RECENT MAJOR CHANGES

Indications and Usage (1.4)	1/2023
Dosage and Administration (2.3)	1/2023
Warning and Precautions (5.4, 5.5)	1/2023

INDICATIONS AND USAGE

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy. (1.1)
  This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Waldenström's macroglobulinemia (WM). (1.2)
- Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti–CD20-based regimen. (1.3)
  This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). (1.4)

DOSAGE AND ADMINISTRATION

- Recommended dosage: 160 mg orally twice daily or 320 mg orally once daily; swallow whole with water and with or without food. (2.1)
- Reduce BRUKINSA dose in patients with severe hepatic impairment. (2.2, 8.7)
- Advise patients not to open, break, or chew capsules. (2.1)
- Manage toxicity using treatment interruption, dose reduction, or discontinuation. (2.4)

DOSAGE FORMS AND STRENGTHS

Capsules: 80 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hemorrhage: Monitor for bleeding and manage appropriately. (5.1)
- Infections: Monitor patients for signs and symptoms of infection, including opportunistic infections, and treat as needed. (5.2)
- Cytopenias: Monitor complete blood counts during treatment. (5.3)
- Second Primary Malignancies: Other malignancies have developed including skin cancers and non-skin carcinomas. Monitor and advise patients to use sun protection. (5.4)
- Cardiac Arrhythmias: Monitor for signs and symptoms of arrhythmias and manage appropriately. (5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of the potential risk to a f etus and to use effective contraception. (5.6)

ADVERSE REACTIONS

The most common adverse reactions (≥30%), including laboratory abnormalities, are neutrophil count decreased, upper respiratory tract infection, platelet count decreased, hemorrhage, and musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BeiGene at 1-877-828-5596 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A Inhibitors: Modify BRUKINSA dose with moderate or strong CYP3A inhibitors as described. (2.3, 7.1)
- CYP3A Inducers: Avoid coadministration with strong or moderate CYP3A inducers. Dose adjustment may be recommended with moderate CYP3A inducers. (2.3, 7.1)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
Revised: 1/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

BRUKINSA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.2 Waldenström's Macroglobulinemia

BRUKINSA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.2)]*.

1.3 Marginal Zone Lymphoma

BRUKINSA is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti–CD20-based regimen.

This indication is approved under accelerated approval based on overall response rate [*see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.4 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

BRUKINSA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of BRUKINSA is 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity.

BRUKINSA can be taken with or without food. Advise patients to swallow capsules whole with water. Advise patients not to open, break, or chew the capsules. If a dose of BRUKINSA is missed, it should be taken as soon as possible on the same day with a return to the normal schedule the following day.

2.2 Dosage Modification for Use in Hepatic Impairment

The recommended dosage of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.3 Dosage Modifications for Drug Interactions

Recommended dosage modifications of BRUKINSA for drug interactions are provided in Table 1 *[see Drug Interactions (7.1)]*.

Table 1: Dosage Modifications for Use with CYP3A Inhibitors or Inducers

Coadministered Drug	Recommended BRUKINSA Dosage (Starting Dose: 160 mg twice daily or 320 mg once daily)
Strong CYP3A inhibitor	80 mg once daily. Interrupt dose as recommended for adverse reactions *[see Dosage and Administration (2.4)]*.
Moderate CYP3A inhibitor	80 mg once daily. Interrupt dose as recommended for adverse reactions *[see Dosage and Administration (2.4)]*.
Strong CYP3A inducer	Avoid concomitant use.
Moderate CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase BRUKINSA dose to 320 mg twice daily.

After discontinuation of a CYP3A inhibitor or moderate CYP3A4 inducer, resume previous dose of BRUKINSA [see Dosage and Administration (2.1, 2.2) and Drug Interactions (7.1)].

2.4 Dosage Modifications for Adverse Reactions

Recommended dosage modifications of BRUKINSA for Grade 3 or higher adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modification for Adverse Reaction

Adverse Reaction	Adverse Reaction Occurrence	Dosage Modification (Starting Dose: 160 mg twice daily or 320 mg once daily)
Hematological toxicities *[see Warnings and Precautions (5.3)]*		
Grade 3 or Grade 4 febrile neutropenia	First	Interrupt BRUKINSA Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 160 mg twice daily or 320 mg once daily.
Platelet count decreased to 25,000-50,000/mm^3 with significant bleeding	Second	Interrupt BRUKINSA Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg twice daily or 160 mg once daily.
Neutrophil count decreased to <500/mm^3 (lasting more than 10 consecutive days)	Third	Interrupt BRUKINSA Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg once daily.
Platelet count decreased to <25,000/mm^3 (lasting more than 10 consecutive days)	Fourth	Discontinue BRUKINSA
Non-hematological toxicities *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*		
Severe or life-threatening non-hematological toxicities[a]	First	Interrupt BRUKINSA Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 160 mg twice daily or 320 mg once daily.a
	Second	Interrupt BRUKINSA Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg twice daily or 160 mg once daily.
	Third	Interrupt BRUKINSA Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg once daily.
	Fourth	Discontinue BRUKINSA

a Evaluate the benefit-risk before resuming treatment at the same dosage for Grade 4 non-hematological toxicity.

Asymptomatic lymphocytosis should not be regarded as an adverse reaction, and these patients should continue taking BRUKINSA.

3 DOSAGE FORMS AND STRENGTHS

Capsules: Each 80 mg capsule is a size 0, white to off-white opaque capsule marked with "ZANU 80" in black ink.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax was reported in 3.6% of patients treated with BRUKINSA monotherapy in clinical trials, with fatalities occurring in 0.3% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 30% of patients.

Bleeding has occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Coadministration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 24% of patients, most commonly pneumonia (11%), with fatal infections occurring in 2.9% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jirovecii pneumonia, and

other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (22%), thrombocytopenia (8%), and anemia (7%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*. Grade 4 neutropenia occurred in 11% of patients, and Grade 4 thrombocytopenia occurred in 2.8% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dosage and Administration (2.4)*]. Treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 13% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer, reported in 7% of patients. Other second primary malignancies included malignant solid tumors (5%), melanoma (1.2%), and hematologic malignancies (0.5%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

5.5 Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 3.7% of 1550 patients treated with BRUKINSA monotherapy, including Grade 3 or higher cases in 1.7% of patients. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher ventricular arrhythmias were reported in 0.2% of patients.

Monitor for signs and symptoms of cardiac arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately *[see Dosage and Administration (2.4)]*, and consider the risks and benefits of continued BRUKINSA treatment.

5.6 Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for 1 week after the last dose. Advise men to avoid fathering a child during treatment and for 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Second Primary Malignancies [*see Warnings and Precautions (5.4)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA as a single-agent in nine clinical trials, administered at 160 mg twice daily in 1445 patients and at 320 mg once daily in 105 patients. Among these 1550 patients, the median duration of exposure was 26 months, 80% of patients were exposed for at least 12 months, and 58% of patients were exposed for at least 24 months.

In this pooled safety population, the most common adverse reactions (≥30%), including laboratory abnormalities, included neutrophil count decreased (42%), upper respiratory tract infection (39%), platelet count decreased (34%), hemorrhage (30%), and musculoskeletal pain (30%).

Mantle Cell Lymphoma (MCL)

The safety of BRUKINSA was evaluated in 118 patients with MCL who received at least one prior therapy in two single-arm clinical trials, BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120] *[see Clinical Studies (14.1)]*. The median age of patients who received BRUKINSA in studies BGB-3111-206 and BGB-3111-AU-003 was 62 years (range: 34 to 86), 75% were male, 75% were Asian, 21% were White, and 94% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count ≥75 × 109/L and an absolute neutrophil count ≥1 × 109/L independent of growth factor support, hepatic enzymes ≤2.5 × upper limit of normal, total bilirubin ≤1.5 × ULN. The BGB-3111-AU-003 trial required a platelet count ≥50 × 109/L and an absolute neutrophil count ≥1 × 109/L independent of growth factor support, hepatic enzymes ≤3 × upper limit of normal, total bilirubin ≤1.5 × ULN. Both trials required a CLcr ≥30 mL/min. Both trials excluded patients with prior allogeneic hematopoietic stem cell transplant, exposure to a BTK inhibitor, known infection with HIV, and serologic evidence of active hepatitis B or hepatitis C infection, and patients requiring strong CYP3A inhibitors or strong CYP3A inducers. Patients received BRUKINSA 160 mg twice daily or 320 mg once daily. Among patients receiving BRUKINSA, 79% were exposed for 6 months or longer, and 68% were exposed for greater than one year.

Fatal events within 30 days of the last dose of BRUKINSA occurred in 8 (7%) of 118 patients with MCL. Fatal cases included pneumonia in 2 patients and cerebral hemorrhage in one patient.

Serious adverse reactions were reported in 36 patients (31%). The most frequent serious adverse reactions that occurred were pneumonia (11%) and hemorrhage (5%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Table 3 summarizes the adverse reactions in BGB-3111-206 and BGB-3111-AU-003.

Table 3: Adverse Reactions (≥10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials

Body System	Adverse Reaction	Percent of Patients (N=118)	
		All Grades %	Grade 3 or Higher %
Infections and infestations	Upper respiratory tract infection[a]	39	0
	Pneumonia[b]	15	10[c]
	Urinary tract infection	11	0.8
Skin and subcutaneous tissue disorders	Rash[d]	36	0
	Bruising[e]	14	0
Gastrointestinal disorders	Diarrhea	23	0.8
	Constipation	13	0
Vascular disorders	Hypertension	12	3.4
	Hemorrhage[f]	11	3.4[c]
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[g]	14	3.4
Respiratory, thoracic and mediastinal disorders	Cough	12	0

a Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral.

b Pneumonia includes pneumonia, pneumonia fungal, pneumonia cryptococcal, pneumonia streptococcal, atypical pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection viral.

c Includes fatal adverse reaction.

d Rash includes all related terms containing rash.

e Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis.

f Hemorrhage includes all related terms containing hemorrhage, hematoma.

g Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis.

Other clinically significant adverse reactions that occurred in <10% of patients with mantle cell lymphoma include major hemorrhage (defined as ≥ Grade 3 hemorrhage or CNS hemorrhage of any grade) (5%), and headache (4.2%).

Table 4: Selected Laboratory Abnormalities[a] (>20%) in Patients with MCL in Studies BGB-3111-206 and BGB-3111-AU-003

Laboratory Parameter	Percent of Patients (N=118)	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	45	20
Lymphocytosis[b]	41	16
Platelets decreased	40	7
Hemoglobin decreased	27	6
Chemistry abnormalities		
Blood uric acid increased	29	2.6
ALT increased	28	0.9
Bilirubin increased	24	0.9

[a] Based on laboratory measurements.

[b] Asymptomatic lymphocytosis is a known effect of BTK inhibition.

Waldenström's Macroglobulinemia (WM)

The safety of BRUKINSA was investigated in two cohorts of Study BGB-3111-302 (ASPEN). Cohort 1 included 199 patients with MYD88 mutation (MYD88MUT) WM, randomized to and treated with either BRUKINSA (101 patients) or ibrutinib (98 patients). The trial also included a non-randomized arm, Cohort 2, with 26 wild type MYD88 (MYD88WT) WM patients and 2 patients with unknown MYD88 status *[see Clinical Studies (14.2)]*.

Among patients who received BRUKINSA, 93% were exposed for 6 months or longer, and 89% were exposed for greater than 1 year.

In Cohort 1 of the ASPEN study safety population (N=101), the median age of patients who received BRUKINSA was 70 years (45-87 years old); 67% were male, 86% were White, 4% were Asian and 10% were not reported (unknown race). In Cohort 2 of the ASPEN study safety population (N=28), the median age of patients who received BRUKINSA was 72 (39-87 years old); 50% were male, 96% were White and 4% were not reported (unknown race).

In Cohort 1, serious adverse reactions occurred in 44% of patients who received BRUKINSA. Serious adverse reactions in >2% of patients included influenza (3%), pneumonia (4%), neutropenia and neutrophil count decreased (3%), hemorrhage (4%), pyrexia (3%), and febrile neutropenia (3%). In Cohort 2, serious adverse reactions occurred in 39% of patients. Serious adverse reactions in >2 patients included pneumonia (14%).

Permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 2% of patients in Cohort 1 and included hemorrhage (1 patient), neutropenia and neutrophil count decreased (1 patient); in Cohort 2, permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 7% of patients and included subdural hemorrhage (1 patient) and diarrhea (1 patient).

Dosage interruptions of BRUKINSA due to an adverse reaction occurred in 32% of patients in Cohort 1 and in 29% in Cohort 2. Adverse reactions which required dosage interruption in >2% of patients included neutropenia, vomiting, hemorrhage, thrombocytopenia, and pneumonia in Cohort 1. Adverse reactions leading to dosage interruption in >2 patients in Cohort 2 included pneumonia and pyrexia.

Dose reductions of BRUKINSA due to an adverse reaction occurred in 11% of patients in Cohort 1 and in 7% in Cohort 2. Adverse reactions which required dose reductions in >2% of patients included neutropenia in Cohort 1. Adverse reactions leading to dose reduction occurred in 2 patients in Cohort 2 (each with one event: diarrhea and pneumonia).

Table 5 summarizes the adverse reactions in Cohort 1 in ASPEN.

Table 5: Adverse Reactions (≥10%) Occurring in Patients with WM Who Received BRUKINSA in Cohort 1

Body System	Adverse Reaction	BRUKINSA (N=101)		Ibrutinib (N=98)	
		All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection[a]	44	0	40	2
	Pneumonia[b]	12	4	26	10
	Urinary tract infection	11	0	13	2
Gastrointestinal disorders	Diarrhea	22	3	34	2
	Nausea	18	0	13	1
	Constipation	16	0	7	0
	Vomiting	12	0	14	1
General disorders	Fatigue[c]	31	1	25	1
	Pyrexia	16	4	13	2
	Edema peripheral	12	0	20	0
Skin and subcutaneous tissue disorders	Bruising[d]	20	0	34	0
	Rash[e]	29	0	32	0
	Pruritus	11	1	6	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[f]	45	9	39	1
	Muscle spasms	10	0	28	1
Nervous system disorders	Headache	18	1	14	1
	Dizziness	13	1	12	0
Respiratory, thoracic and mediastinal disorders	Cough	16	0	18	0
	Dyspnea	14	0	7	0
Vascular disorders	Hemorrhage[g]	42	4	43	9
	Hypertension	14	9	19	14

a Upper respiratory tract infection includes upper respiratory tract infection, laryngitis, nasopharyngitis, sinusitis, rhinitis, viral upper respiratory tract infection, pharyngitis, rhinovirus infection, upper respiratory tract congestion.

b Pneumonia includes lower respiratory tract infection, lung infiltration, pneumonia, pneumonia aspiration, pneumonia viral.

c Fatigue includes asthenia, fatigue, lethargy.

d Bruising includes all related terms containing bruise, contusion, or ecchymosis.

e Rash includes all related terms rash, maculo-papular rash, erythema, rash erythematous, drug eruption, dermatitis allergic, dermatitis atopic, rash pruritic, dermatitis, photodermatoses, dermatitis acneiform, stasis dermatitis, vasculitic rash, eyelid rash, urticaria, skin toxicity.

f Musculoskeletal pain includes back pain, arthralgia, pain in extremity, musculoskeletal pain, myalgia, bone pain, spinal pain, musculoskeletal chest pain, neck pain, arthritis, musculoskeletal discomfort.

g Hemorrhage includes epistaxis, hematuria, conjunctival hemorrhage, hematoma, rectal hemorrhage, periorbital hemorrhage, mouth hemorrhage, post-procedural hemorrhage, hemoptysis, skin hemorrhage, hemorrhoidal hemorrhage, ear hemorrhage, eye hemorrhage, hemorrhagic diathesis, periorbital hematoma, subdural hemorrhage, wound hemorrhage, gastric hemorrhage, lower gastrointestinal hemorrhage, spontaneous hematoma, traumatic hematoma, traumatic intracranial hemorrhage, tumor hemorrhage, retinal hemorrhage, hematochezia, diarrhea hemorrhagic, hemorrhage, melena, post-procedural hematoma, subdural hematoma, anal hemorrhage, hemorrhagic disorder, pericardial hemorrhage, postmenopausal hemorrhage, stoma site hemorrhage, subarachnoid hemorrhage.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included localized infection, atrial fibrillation or atrial flutter, and hematuria.

Table 6 summarizes the laboratory abnormalities in ASPEN.

Table 6: Select Laboratory Abnormalities[a] (≥20%) that Worsened from Baseline in Patients with WM Who Received BRUKINSA in Cohort 1

Laboratory Abnormality	BRUKINSA[b]		Ibrutinib[b]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	50	24	34	9
Platelets decreased	35	8	39	5
Hemoglobin decreased	20	7	20	7
Chemistry abnormalities				
Glucose increased	45	2.3	33	2.3
Creatinine increased	31	1	21	1
Calcium decreased	27	2	26	0
Potassium increased	24	2	12	0
Phosphate decreased	20	3.1	18	0
Urate increased	16	3.2	34	6
Bilirubin increased	12	1	33	1

a Based on laboratory measurements.

b The denominator used to calculate the rate varied from 86 to 101 based on the number of patients with a baseline value and at least one post-treatment value.

Marginal Zone Lymphoma

The safety of BRUKINSA was evaluated in 88 patients with previously treated MZL in two single-arm clinical studies, BGB-3111-214 and BGB-3111-AU-003 [see Clinical Studies (14.3)]. The trials required an absolute neutrophil count ≥1 × 109/L, platelet count ≥50 or ≥75 × 109/L and adequate hepatic function and excluded patients requiring a strong CYP3A inhibitor or inducer. Patients received BRUKINSA 160 mg twice daily (97%) or 320 mg once daily (3%). The median age in both studies combined was 70 years (range: 37 to 95), 52% were male, 64% were Caucasian and 19% were Asian. Most patients (92%) had an ECOG performance status of 0 to 1. Eighty percent received BRUKINSA for 6 months or longer, and 67% received treatment for more than one year.

Two fatal adverse reactions (2.3%) occurred within 30 days of the last dose of BRUKINSA, including myocardial infarction and a Covid-19–related death.

Serious adverse reactions occurred in 40% of patients. The most frequent serious adverse reactions were pyrexia (8%) and pneumonia (7%).

Adverse reactions lead to treatment discontinuation in 6% of patients, dose reduction in 2.3%, and dose interruption in 34%. The leading cause of dose modification was respiratory tract infections (13%).

Table 7 summarizes selected adverse reactions in BGB-3111-214 and BGB-3111-AU-003.

Table 7: Adverse Reactions Occurring in ≥10% Patients with MZL Who Received BRUKINSA

Body System	Adverse Reaction	BRUKINSA (N=88)	
		All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection[a]	26	3.4
	Urinary tract infection[b]	11	2.3
	Pneumonia[c,d]	10	6
Gastrointestinal disorders	Diarrhea[e]	25	3.4
	Abdominal pain[f]	14	2.3
	Nausea	13	0
Skin and subcutaneous tissue disorders	Bruising[g]	24	0
	Rash[h]	21	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[i]	27	1.1
Vascular disorders	Hemorrhage[j]	23	1.1
General disorders	Fatigue[k]	21	2.3
Respiratory, thoracic and mediastinal disorders	Cough[l]	10	0

a Upper respiratory tract infection includes upper respiratory tract infection, nasopharyngitis, sinusitis, tonsillitis, rhinitis, viral upper respiratory tract infection.

b Urinary tract infection includes urinary tract infection, cystitis, Escherichia urinary tract infection, pyelonephritis, cystitis.

c Pneumonia includes COVID-19 pneumonia, pneumonia, bronchopulmonary aspergillosis, lower respiratory tract infection, organizing pneumonia.

d Includes 2 fatalities from COVID-19 pneumonia.

e Diarrhea includes diarrhea and diarrhea hemorrhagic.

f Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort.

g Bruising includes contusion, ecchymosis, increased tendency to bruise, post procedural contusion.

h Rash includes rash, rash maculo-papular, rash pruritic, dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, drug reaction with eosinophilia and systemic symptoms, erythema, photosensitivity reaction, rash erythematous, rash papular, seborrheic dermatitis.

i Musculoskeletal pain includes back pain, arthralgia, musculoskeletal pain, myalgia, pain in extremity, musculoskeletal chest pain, bone pain, musculoskeletal discomfort, neck pain.

j Hemorrhage includes epistaxis, hematuria, hemorrhoidal hemorrhage, hematoma, hemoptysis, conjunctival hemorrhage, diarrhea hemorrhagic, hemorrhage urinary tract, mouth hemorrhage, pulmonary hematoma, subcutaneous hematoma, gingival bleeding, melena, upper gastrointestinal hemorrhage.

k Fatigue includes fatigue, lethargy, asthenia.

l Cough includes cough and productive cough

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included peripheral neuropathy, second primary malignancies, dizziness, edema, headache, petechiae, purpura, and atrial fibrillation or flutter.

Table 8 summarizes select laboratory abnormalities.

Table 8: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with MZL

Laboratory Abnormality[a]	BRUKINSA	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	43	15
Platelets decreased	33	10
Lymphocytes decreased	32	8
Hemoglobin decreased	26	6
Chemistry abnormalities		
Glucose increased	54	4.6
Creatinine increased	34	1.1
Phosphate decreased	27	2.3
Calcium decreased	23	0
ALT increased	22	1.1

a The denominator used to calculate the rate varied from 87 to 88 based on the number of patients with a baseline value and at least one post-treatment value.

Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

The safety data described below reflect exposure to BRUKINSA (160 mg twice daily) in 675 patients with CLL from two randomized controlled clinical trials [see Clinical Studies (14.4)]. The trial required patients to be unsuitable for fludarabine, cyclophosphamide, and rituximab (FCR) therapy defined as age ≥65 years, or age 18 to <65 years with either a total Cumulative Illness Rating Scale (CIRS) >6, creatinine clearance 30 to 69 mL/min, or history of serious or frequent infections. The trial excluded patients with AST or ALT ≥2 times the upper limit of normal (ULN) or bilirubin ≥3 times (ULN) and patients requiring a strong CYP3A inhibitor or inducer.

SEQUOIA

The safety of BRUKINSA monotherapy in patients with previously untreated CLL/SLL was evaluated in a randomized, multicenter, open-label, actively controlled trial [see Clinical Studies (14.4)]. Patients without deletion of chromosome 17p13.1 (17p deletion) (Cohort 1) received either BRUKINSA 160 mg twice daily until disease progression or unacceptable toxicity (n=240) or bendamustine plus rituximab (BR) for 6 cycles (n=227). Bendamustine was dosed at 90 mg/m2/day intravenously on the first 2 days of each cycle, and rituximab was dosed at 375 mg/m2 on day 1 of Cycle 1 and 500 mg/m2 on day 1 of Cycles 2 to 6.

Additionally, the same BRUKINSA regimen was evaluated in 111 patients with previously untreated CLL/SLL with 17p deletion in a non-randomized single arm (Cohort 2).

Randomized cohort: previously untreated CLL/SLL without 17p deletion

In patients with previously untreated CLL/SLL without 17p deletion, the median age was 70, 62% were male, 89% were White, 2% were Asian, and 2% were Black. Most patients (93%) had an ECOG performance status of 0 to 1.

The median duration of exposure to BRUKINSA was 26 months, with 71% exposed for more than 2 years.

Serious adverse reactions occurred in 36% of patients who received BRUKINSA. Serious adverse reactions that occurred in ≥5% of patients were COVID-19, pneumonia, and second primary malignancy (5% each). Fatal adverse reactions occurred in 11 (4.6%) patients with the leading cause of death being COVID-19 (2.1%).

Adverse reactions led to permanent discontinuation of BRUKINSA in 8% of patients, dose reduction in 8%, and dose interruption in 46%. The most common adverse reactions leading to permanent discontinuation were second primary malignancy and COVID-19. The leading causes of dose modification (≥5% of all patients) were respiratory infections (COVID-19, pneumonia) and hemorrhage.

Table 9 summarizes select adverse reactions in this randomized cohort

Table 9: Adverse Reactions in ≥10% Patients with Previously Untreated CLL/SLL Without 17p Deletion in SEQUOIA

System Organ Class Preferred Term	CLL/SLL without 17p deletion			
	BRUKINSA (N=240)		BR (N=227)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[a]	33	1.7	17	0.4
Infections and infestations				
Upper respiratory tract infection[b]	28	1.3	15	0.9
Pneumonia[c]	13*	5	8†	4
Vascular disorders				
Hemorrhage[d]	27*	4	4	0.4
Hypertension[e]	14	7	5	2.6
Skin and subcutaneous tissue disorders				
Rash[f]	24	1.3	30	5
Bruising[g]	24	0	2.6	0
Respiratory, thoracic and mediastinal disorders				
Cough[e]	15	0	10	0
Gastrointestinal disorders				
Diarrhea	14	0.8	12†	0.9
Constipation	10	0.4	18	0.0
Nausea	10	0	33	1.3
General disorders				
Fatigue[h]	14	1.3	21	1.8
Neoplasms				
Second primary malignancy[i]	13*	6	1.3	0.4
Nervous system disorders				
Headache[e]	12	0	8	0
Dizziness[j]	11	0.8	5	0

* Includes 3 fatal outcomes.

† Includes 2 fatal outcomes.

a Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, spinal pain, musculoskeletal discomfort, bone pain.

b Upper respiratory tract infection: upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, pharyngitis, upper respiratory tract congestion, laryngitis, tonsillitis and upper respiratory tract inflammation, and related terms.

c Pneumonia: pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lung infiltration, and related terms including specific types of infection.

d Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.

e Includes multiple similar adverse reaction terms.

f Rash: rash, dermatitis, drug eruption, and related terms.

g Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.

h Fatigue: fatigue, asthenia, and lethargy

i Second primary malignancy: includes non-melanoma skin cancer, malignant solid tumors (including lung, renal, genitourinary, breast, ovarian, and rectal), and chronic myeloid leukemia.

j Dizziness: dizziness and vertigo.

Other clinically significant adverse reactions occurring in <10% of BRUKINSA recipients in this cohort included COVID-19 (9%), edema (8%), abdominal pain (8%), urinary tract infection (7%), and atrial fibrillation or flutter (3.3%).

Table 10 summarizes select laboratory abnormalities in this cohort.

Table 10: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with Previously Untreated CLL/SLL without 17p Deletion in SEQUOIA

Laboratory Abnormality[a]	BRUKINSA		BR	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	37	15	80	53
Hemoglobin decreased	29	2.5	66	8
Platelets decreased	27	1.7	61	11
Leukocytes increased	21[b]	21	0.4	0.4
Chemistry abnormalities				
Glucose increased[c]	55	7	67	10
Creatinine increased	22	0.8	18	0.4
Magnesium increased	22	0	14	0.4
Alanine aminotransferase increased	21	2.1	23	2.2

a The denominator used to calculate the rate was 239 in the BRUKINSA arm and 227 in the BR arm, based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.

b Lymphocytes increased in 15%.

c Non-fasting conditions.

Single-arm cohort: previously untreated CLL/SLL and 17p deletion

In 111 patients with previously untreated, 17p del CLL/SLL, the median age was 70, 71% were male, 95% were White, and 1% were Asian. Most patients (87%) had an ECOG performance status of 0 to 1. The median duration of exposure to BRUKINSA was 30 months.

Fatal adverse reactions occurred in 3 (2.7%) patients, including pneumonia, renal insufficiency, and aortic dissection (1 patient each).

Serious adverse reactions occurred in 41% of patients treated with BRUKINSA. Serious adverse reactions reported in ≥5% of patients were pneumonia (8%) and second primary malignancy (7%).

Adverse reactions led to treatment discontinuation in 5% of patients, dose reduction in 5%, and dose interruption in 51%. The leading causes of dose modification (≥5% of all patients) were pneumonia, neutropenia, second primary malignancy, and diarrhea.

Table 11 summarizes select adverse reactions in this cohort.

Table 11: Adverse Reactions in ≥10% of Patients with Previously Untreated CLL/SLL and 17p Deletion in SEQUOIA

System Organ Class Preferred Term	CLL/SLL with 17p Deletion	
	BRUKINSA (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations		
Upper respiratory tract infection[a]	38	0.0
Pneumonia[b]	20*	8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[c]	38	2.7
Skin and subcutaneous tissue disorders		
Rash[d]	28	0.0
Bruising[e]	26	0.9
Vascular disorders		
Hemorrhage[f]	28	4.5
Hypertension[g]	11	5.4
Neoplasms		
Second primary malignancy[h]	22†	6
Gastrointestinal disorders		
Diarrhea	18	0.9
Nausea	16	0.0
Constipation	15	0.0
Abdominal pain[g]	12	1.8
Respiratory, thoracic and mediastinal disorders		
Cough[g]	18	0.0
Dyspnea[g]	13	0.0
General disorders and administration site conditions		
Fatigue[i]	14	0.9
Nervous system disorders		
Headache	11	1.8

* Includes 1 fatal outcome.

† Includes non-melanoma skin cancer in 13%.

a Upper respiratory tract infection: upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, pharyngitis, upper respiratory tract congestion, upper respiratory tract inflammation, viral upper respiratory tract infection, and related terms.

b Pneumonia: pneumonia, COVID-19 pneumonia, lower respiratory tract infection, and related terms including specific types of infection.

c Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, bone pain.

d Rash: rash, dermatitis, toxic skin eruption, and related terms.

e Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.

f Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.

g Includes multiple similar adverse reaction terms.

h Second primary malignancy: includes non-melanoma skin cancer, malignant solid tumors (including bladder, lung, renal, breast, prostate, ovarian, pelvis, and ureter), and malignant melanoma.

i Fatigue: fatigue, asthenia, and lethargy.

Clinically significant adverse reactions occurring in <10% of BRUKINSA recipients in this cohort included urinary tract infection (8%), edema (7%), atrial fibrillation or flutter (4.5%), and COVID-19 (3.6%).

Table 12 summarizes select laboratory abnormalities in this cohort.

Table 12: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with Previously Untreated CLL/SLL and 17p Deletion in SEQUOIA

Laboratory Abnormality[a]	BRUKINSA	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	42	19[b]
Hemoglobin decreased	26	3.6
Platelets decreased	23	0.9
Chemistry abnormalities		
Glucose increased[c]	52	6
Magnesium increased	31	0
Creatinine increased	27	0.9

a The denominator used to calculate the rate varied from 110 to 111 based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.

b Grade 4, 9%.

c Non-fasting conditions.

ALPINE

The safety of BRUKINSA monotherapy was evaluated in patients with previously treated CLL/SLL in a randomized, multicenter, open-label, actively controlled trial *[see Clinical Studies (14.4)]*. In ALPINE, 324 patients received BRUKINSA monotherapy, 160 mg orally twice daily and 324 patients received ibrutinib monotherapy, 420 mg orally daily until disease progression or unacceptable toxicity.

In ALPINE, the median duration of exposure was 24 months for BRUKINSA. Adverse reactions leading to death in the BRUKINSA arm occurred in 24 (7%) patients. Adverse reactions leading to death that occurred in >1% of patients were pneumonia (2.8%) and COVID-19 infection (1.9%).

One hundred and four patients in the BRUKINSA arm (32%) reported ≥1 serious adverse reaction. Serious adverse reactions occurring in ≥5% of patients were pneumonia (10%), COVID-19 (7%), and second primary malignancies (5%).

Adverse reactions led to treatment discontinuation in 13% of patients, dose reduction in 11%, and dose interruption in 42%. The leading cause of treatment discontinuation was pneumonia. The leading causes of dose modification (≥5% of all patients) were respiratory infections (COVID-19, pneumonia) and neutropenia.

Table 13 summarizes select adverse reactions in ALPINE.

Table 13: Adverse Reactions in ≥10% of Patients with Relapsed or Refractory CLL/SLL Who Received BRUKINSA in ALPINE

System Organ Class Preferred Term	BRUKINSA (N=324)		Ibrutinib (N=324)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations				
Upper respiratory tract infection[a]	27	1.2	22	1.2
Pneumonia[b]	18*	9	19†	11
COVID-19[c]	14*	7	10†	4.6
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[d]	26	0.6	28	0.6
Vascular disorders				
Hemorrhage[e]	24*	2.5	26†	3.7
Hypertension[f]	19	13	20	13
Skin and subcutaneous tissue disorders				
Rash[g]	20	1.2	21	0.9
Bruising[h]	16	0.0	14	0.0
Gastrointestinal disorders				
Diarrhea	14	1.5	22	0.9
General disorders				
Fatigue[i]	13	0.9	14	0.9
Respiratory, thoracic and mediastinal disorders				
Cough[f]	11	0.3	11	0.0
Nervous system disorders				
Dizziness[f]	10	0.0	7	0.0

* Includes fatal outcomes: pneumonia (9 patients), COVID-19 (8 patients), and hemorrhage (1 patient).

† Includes fatal outcomes: pneumonia (10 patients), COVID-19 (9 patients), and hemorrhage (2 patients).

a Upper respiratory tract infection: upper respiratory tract infection, sinusitis, pharyngitis, rhinitis, nasopharyngitis, laryngitis, tonsillitis, and related terms.

b Pneumonia: pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lung infiltration, and related terms including specific types of infection.

c COVID-19: COVID-19, COVID-19 pneumonia, post-acute COVID-19 syndrome, SARS-CoV-2 test positive.

d Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, spinal pain, bone pain, and musculoskeletal discomfort.

e Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.

f Includes multiple similar adverse reaction terms.

g Rash: rash, Dermatitis, and related terms.

h Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.

i Fatigue: asthenia, fatigue, lethargy.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included urinary tract infection (9%), supraventricular arrhythmias (9%) including atrial fibrillation or flutter (4.6%), abdominal pain (8%), headache (8%), pruritus (6.2%), constipation (5.9%), and edema (4.6%).

Table 14 summarizes select laboratory abnormalities in ALPINE.

Table 14: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients Who Received BRUKINSA in ALPINE

Laboratory Abnormality[a]	BRUKINSA		Ibrutinib	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	43	15	33	16
Hemoglobin decreased	28	4	32	3.7
Lymphocytes increased	24	19	26	19
Platelets decreased	22	4	24	3.4
Chemistry abnormalities				
Glucose increased	52	5	29	2.8
Creatinine increased	26	0.0	23	0.0
Phosphate decreased	21	2.5	13	2.2
Calcium decreased	21	0.6	29	0.0

a The denominator used to calculate the rate was 321 in the BRUKINSA arm, and varied from 320 to 321 in the ibrutinib arm, based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 15: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Coadministration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may increase the risk of BRUKINSA toxicities.
Prevention or management	• Reduce BRUKINSA dosage when coadministered with moderate or strong CYP3A inhibitors *[see Dosage and Administration (2.3)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Coadministration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may reduce BRUKINSA efficacy.
Prevention or management	• Avoid coadministration of BRUKINSA with strong CYP3A inducers *[see Dosage and Administration (2.3)]*. • Avoid coadministration of BRUKINSA with moderate CYP3A4 inducers *[see Dosage and Administration (2.3)]*. If these inducers cannot be avoided, increase BRUKINSA dosage to 320 mg twice daily [see Dosage and Administration (2.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 5-fold human exposures *(see Data)*. Women should be advised to avoid pregnancy while taking BRUKINSA. If BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2 or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre and postnatal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g., cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for two weeks following the last dose.

8.3 Females and Males of Reproductive Potential

BRUKINSA can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for 1 week following the last dose of BRUKINSA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise men to avoid fathering a child while receiving BRUKINSA and for 1 week following the last dose of BRUKINSA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1550 patients with MCL, MZL, WM, and CLL/SLL in clinical studies with BRUKINSA, 61% were ≥65 years of age, and 22% were ≥75 years of age. Patients ≥65 years of age had numerically higher rates of Grade 3 or higher adverse reactions and serious adverse reactions (63% and 47%, respectively) than patients <65 years of age (57% and 36%, respectively). No overall differences in effectiveness were observed between younger and older patients.

8.6 Renal Impairment

No dosage modification is recommended in patients with mild, moderate, or severe renal impairment (CLcr ≥15 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

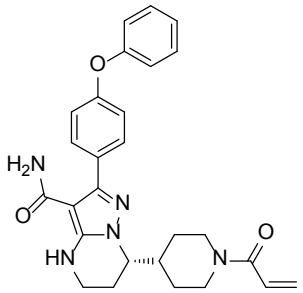
Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment [see Dosage and Administration (2.2)]. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

BRUKINSA (zanubrutinib) is a kinase inhibitor. The empirical formula of zanubrutinib is C27H29N5O3 and the chemical name is (S)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide. Zanubrutinib is a white to off-white powder, with a pH of 7.8 in saturated solution. The aqueous solubility of zanubrutinib is pH dependent, from very slightly soluble to practically insoluble.

The molecular weight of zanubrutinib is 471.55 Daltons.

Zanubrutinib has the following structure:



Each BRUKINSA capsule for oral administration contains 80 mg zanubrutinib and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. The capsule shell contains edible black ink, gelatin, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zanubrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Zanubrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis and adhesion. In nonclinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumor growth.

12.2 Pharmacodynamics

BTK Occupancy in PBMCs and Lymph Nodes

The median steady-state BTK occupancy in peripheral blood mononuclear cells was maintained at 100% over 24 hours at a total daily dose of 320 mg in patients with B-cell malignancies. The median steady-state BTK occupancy in lymph nodes was 94% to 100% following the approved recommended dosage.

Cardiac Electrophysiology

At the approved recommended doses (160 mg twice daily or 320 mg once daily), there were no clinically relevant effects on the QTc interval. The effect of BRUKINSA on the QTc interval above the therapeutic exposure has not been evaluated.

12.3 Pharmacokinetics

Zanubrutinib maximum plasma concentration (Cmax) and area under the plasma drug concentration over time curve (AUC) increase proportionally over a dosage range from 40 mg to 320 mg (0.13 to 1 time the recommended total daily dose). Limited systemic accumulation of zanubrutinib was observed following repeated administration.

The geometric mean (%CV) zanubrutinib steady-state daily AUC is 2,099 (42%) ng·h/mL following 160 mg twice daily and 1,917 (59%) ng·h/mL following 320 mg once daily. The geometric mean (%CV) zanubrutinib steady-state Cmax is 295 (55%) ng/mL following 160 mg twice daily and 537 (55%) ng/mL following 320 mg once daily.

Absorption

The median tmax of zanubrutinib is 2 hours.

Effect of Food

No clinically significant differences in zanubrutinib AUC or Cmax were observed following the administration of a high-fat meal (approximately 1,000 calories with 50% of total caloric content from fat) in healthy subjects.

Distribution

The geometric mean (%CV) apparent volume of distribution (Vz/F) of zanubrutinib is 537 (73%) L. The plasma protein binding of zanubrutinib is approximately 94% and the blood-to-plasma ratio is 0.7 to 0.8.

Elimination

The mean half-life (t½) of zanubrutinib is approximately 2 to 4 hours following a single oral zanubrutinib dose of 160 mg or 320 mg. The geometric mean (%CV) apparent oral clearance (CL/F) of zanubrutinib is 128 (58%) L/h.

Metabolism

Zanubrutinib is primarily metabolized by cytochrome P450(CYP)3A.

Excretion

Following a single radiolabeled zanubrutinib dose of 320 mg to healthy subjects, approximately 87% of the dose was recovered in feces (38% unchanged) and 8% in urine (less than 1% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of zanubrutinib were observed based on age (19 to 90 years), sex, race (Asian, Caucasian, and Other), body weight (36 to 144 kg) or mild, moderate or severe renal impairment (creatinine clearance [CLcr] ≥15 mL/min as estimated by Cockcroft-Gault). The effect of dialysis on zanubrutinib pharmacokinetics is unknown.

Hepatic Impairment

The total AUC of zanubrutinib increased by 11% in subjects with mild hepatic impairment (Child-Pugh class A), by 21% in subjects with moderate hepatic impairment (Child-Pugh class B), and by 60% in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function. The unbound AUC of zanubrutinib increased by 23% in subjects with mild hepatic impairment (Child-Pugh class A), by 43% in subjects with moderate hepatic impairment (Child-Pugh class B) and by 194% in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

CYP3A Inhibitors: Coadministration of multiple doses of CYP3A inhibitors increases zanubrutinib Cmax and AUC (Table 16).

Table 16: Observed or Predicted Increase in Zanubrutinib Exposure After Coadministration of CYP3A Inhibitors

Coadministered CYP3A Inhibitor	Increase in Zanubrutinib C_{max}	Increase in Zanubrutinib AUC
	Observed	
Itraconazole (200 mg once daily)	157%	278%
	Predicted	
Clarithromycin (250 mg twice daily)	175%	183%
Diltiazem (60 mg three times daily)	151%	157%
Erythromycin (500 mg four times daily)	284%	317%
Fluconazole (200 mg once daily)	179%	177%
Fluconazole (400 mg once daily)	270%	284%

CYP3A Inducers: Coadministration of multiple doses of rifampin (strong CYP3A inducer) decreased the zanubrutinib Cmax by 92% and AUC by 93%. Coadministration of multiple doses of rifabutin (moderate CYP3A inducer) decreased the zanubrutinib Cmax by 48% and AUC by 44%.

Coadministration of multiple doses of efavirenz (moderate CYP3A inducer) is predicted to decrease zanubrutinib Cmax by 58% and AUC by 60%.

CYP3A Substrates: Coadministration of multiple doses of zanubrutinib decreased midazolam (CYP3A substrate) Cmax by 30% and AUC by 47%.

CYP2C19 Substrates: Coadministration of multiple doses of zanubrutinib decreased omeprazole (CYP2C19 substrate) Cmax by 20% and AUC by 36%.

Other CYP Substrates: No clinically significant differences were observed with warfarin (CYP2C9 substrate) pharmacokinetics when coadministered with zanubrutinib.

Transporter Systems: Coadministration of multiple doses of zanubrutinib increased digoxin (P gp substrate) Cmax by 34% and AUC by 11%. No clinically significant differences in the pharmacokinetics of rosuvastatin (BCRP substrate) were observed when coadministered with zanubrutinib.

Gastric Acid Reducing Agents: No clinically significant differences in zanubrutinib pharmacokinetics were observed when coadministered with gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists).

In Vitro Studies

CYP Enzymes: Zanubrutinib is an inducer of CYP2B6 and CYP2C8.

Transporter Systems: Zanubrutinib is likely to be a substrate of P-gp. Zanubrutinib is not a substrate or inhibitor of OAT1, OAT3, OCT2, OATP1B1, or OATP1B3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with zanubrutinib.

Zanubrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in rats.

A combined male and female fertility and early embryonic development study was conducted in rats at oral zanubrutinib doses of 30 to 300 mg/kg/day. Male rats were dosed 4 weeks prior to mating and through mating and female rats were dosed 2 weeks prior to mating and to gestation day 7. No effect on male or female fertility was noted but at the highest dose tested, morphological abnormalities in sperm and increased post-implantation loss were noted. The high dose of 300 mg/kg/day is approximately 10 times the human recommended dose, based on body surface area.

14 CLINICAL STUDIES

14.1 Mantle Cell Lymphoma

The efficacy of BRUKINSA was assessed in BGB-3111-206 [NCT03206970], a Phase 2, open-label, multicenter, single-arm trial of 86 previously treated patients with MCL who had received at least one prior therapy. BRUKINSA was given orally at a dose of 160 mg twice daily until disease progression or unacceptable toxicity.

The median age of patients was 60.5 years (range: 34 to 75) and the majority were male (78%). The median time since diagnosis to study entry was 30 months (range: 3 to 102) and the median number of prior therapies was 2 (range: 1 to 4). The most common prior regimens were CHOP-based (91%) followed by rituximab-based (74%). The majority of patients had extranodal involvement (71%) and refractory disease (52%). Blastoid variant of MCL was present in 14% of patients. The MIPI score was low in 58%, intermediate in 29%, and high risk in 13%.

The efficacy of BRUKINSA was also assessed in BGB-3111-AU-003 [NCT02343120], a Phase 1/2, open-label, dose-escalation, global, multicenter, single-arm trial of B cell malignancies including 32 previously treated MCL patients treated with BRUKINSA. BRUKINSA was given orally at doses of 160 mg twice daily or 320 mg daily. The median age of patients with previously treated MCL was 70 years (range: 42 to 86) and 38% of patients were ≥75 years old. Most patients were male (69%) and Caucasian (78%). The MIPI score was low in 28%, intermediate in 41%, and high risk in 31%.

Tumor response was according to the 2014 Lugano Classification for both studies, and the primary efficacy endpoint was overall response rate as assessed by an Independent Review Committee.

Table 17: Efficacy Results in Patients with MCL by Independent Review Committee

	Study BGB-3111-206 (N=86)	Study BGB-3111-AU-003 (N=32)
ORR (95% CI)	84% (74, 91)	84% (67, 95)
CR	59%	22%[a]
PR	24%	62%
Median DoR in months (95% CI)	19.5 (16.6, NE)	18.5 (12.6, NE)

ORR: overall response rate, CR: complete response, PR: partial response, DoR: duration of response, CI: confidence interval, NE: not estimable.

a FDG-PET scans were not required for response assessment.

14.2 Waldenström's Macroglobulinemia

The efficacy of BRUKINSA was evaluated in ASPEN [NCT03053440], a randomized, active control, open-label trial, comparing BRUKINSA and ibrutinib in patients with MYD88 L265P mutation ($MYD88^{MUT}$) WM. Patients in Cohort 1 (n=201) were randomized 1:1 to receive BRUKINSA 160 mg twice daily or ibrutinib 420 mg once daily until disease progression or unacceptable toxicity. Randomization was stratified by number of prior therapies (0 versus 1-3 versus >3) and CXCR4 status (presence or absence of a WHIM-like mutation as measured by Sanger assay).

The major efficacy outcome was the response rate defined as PR or better as assessed by IRC based on standard consensus response criteria from the International Workshop on Waldenström's Macroglobulinemia (IWWM)-6 criteria. An additional efficacy outcome measure was duration of response (DOR).

The median age was 70 years (range: 38 to 90) and 68% were male. Of those enrolled, 2% were Asian, 91% were White, and 7% were of unknown race. ECOG performance status of 0 or 1 was present in 93% patients at baseline and 7% had a baseline ECOG performance status of 2. A total of 82% had relapsed/refractory disease with 85% having received prior alkylating agents and 91% prior anti-CD20 therapy. The median number of prior therapies in those with relapsed/refractory disease was 1 (range: 1 to 8). A total of 91 (45%) patients had International Prognostic Scoring System (IPSS) high WM.

The study did not meet statistical significance for the prespecified efficacy outcome of superior CR+VGPR as assessed by IRC, tested first in patients with R/R disease in ASPEN.

Table 18 shows the response rates in ASPEN based on IRC assessment.

Table 18: Response Rate and Duration of Response Based on IRC Assessment in ASPEN

	Standard IWWM-6[a]		Modified IWWM-6[b]	
Response Category	**BRUKINSA (N=102)**	**Ibrutinib**	**BRUKINSA (N=102)**	**Ibrutinib**
Response rate (CR+VGPR+PR), (%)	79 (77.5)	77 (77.8)	79 (77.5)	77 (77.8)
95% CI (%)[c]	(68.1, 85.1)	(68.3, 85.5)	(68.1, 85.1)	(68.3, 85.5)
Complete Response (CR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very Good Partial Response (VGPR)	16 (15.7)	7 (7.1)	29 (28.4)	19 (19.2)
Partial Response (PR), (%)	63 (61.8)	70 (70.7)	50 (49.0)	58 (58.6)
Duration of response (DOR), Event-free at 12 months (95% CI)[d]	94.4% (85.8, 97.9)	87.9% (77.0, 93.8)	94.4% (85.8, 97.9)	87.9% (77.0, 93.8)

a IWWM-6 criteria (Owen et al, 2013) require complete resolution of extramedullary disease (EMD) if present at baseline for VGPR to be assessed.

b Modified IWWM-6 criteria (Treon, 2015) require a reduction in EMD if present at baseline for VGPR to be assessed.

c 2-sided Clopper-Pearson 95% confidence interval.

d Estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

ASPEN Cohort 2

Cohort 2 enrolled patients with MYD88 wildtype ($MYD88^{WT}$) or MYD88 mutation unknown WM (N=26 and 2, respectively) and received BRUKINSA 160 mg twice daily. The median age was 72 years (range: 39 to 87) with 43% >75 years, 50% were male, 96% were White, and 4% were not reported (unknown race). 86% patients had a baseline ECOG performance status 0 or 1 and 14% had a baseline performance status of 2. Twenty-three of the 28 patients in Cohort 2 had relapsed or refractory disease.

In Cohort 2, response (CR+VGPR+PR) as assessed by IRC using IWWM-6 or modified IWWM-6 was seen in 50% (13 out of 26 response evaluable patients; 95% CI: 29.9, 70.1).

14.3 Marginal Zone Lymphoma

The efficacy of BRUKINSA was assessed in Study BGB-3111-214 [NCT03846427], an open-label, multicenter, single-arm trial that evaluated 66 patients with MZL who received at least one prior anti–CD20-based therapy. BRUKINSA was given orally at a dosage of 160 mg twice daily until disease progression or unacceptable toxicity. The median age was 70 years (range: 37 to 85); 55% were male; 38% had extranodal MZL, 38% nodal, 18% splenic and 6% had unknown subtype. The median number of prior systemic therapies was 2 (range: 1 to 6), with 27% having 3 or more lines of systemic therapy; 88% had prior rituximab-based chemotherapy; 32% had refractory disease at study entry.

The efficacy of BRUKINSA was also assessed in BGB-3111-AU-003 [NCT02343120], an open-label, multicenter, single-arm trial that included 20 patients with previously treated MZL (45% having extranodal MZL, 25% nodal, 30% splenic). BRUKINSA was given orally at dosages of 160 mg twice daily or 320 mg once daily. The median age was 70 years (range: 52 to 85); 50% were male. The median number of prior systemic therapies was 2 (range: 1 to 5), with 20% having 3 or more lines of systemic therapy; 95% had prior rituximab-based chemotherapy.

Efficacy was based on overall response rate (ORR) and duration of response as assessed by an Independent Review Committee (IRC) using 2014 Lugano criteria (Table 19).

Table 19: Efficacy Results per IRC in Patients with MZL

Parameter	**Study BGB-3111-214 (N=66)**	**Study BGB-3111-AU-003 (N=20)**
Overall Response Rate (CT-based)[a]		
ORR, n	37 (56%)	16 (80%)
(95% CI, %)	(43, 68)	(56, 94)
CR, n	13 (20%)	4 (20%)
PR, n	24 (36%)	12 (60%)
Time to Response		
Median (range), months	2.9 (1.8, 11.1)	2.9 (2.6, 23.1)
Duration of Response[b]		
Median DoR (95% CI), months	NE (NE, NE)	NE (8.4, NE)
Rate at 12 months (95% CI)	85% (67, 93)	72% (40, 88)

ORR: overall response rate, CR: complete response, PR: partial response, DoR: duration of response, CI: confidence interval, NE: not estimable

a Per 2014 CT-based Lugano criteria. FDG-PET scans were not considered for this response assessment.

b Based on Kaplan-Meier estimation. Estimated median follow-up for DoR was 8.3 months for Study BGB-3111-214 and 31.4 months for Study BGB-3111-AU-003.

In study BGB-3111-214, ORR prioritizing PET-CT when available (55 patients, with the remainder assessed by CT scan) was 67% (95% CI: 54, 78) with a CR rate of 26%.

14.4 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

The efficacy of BRUKINSA in patients with CLL/SLL was evaluated in two randomized controlled trials.

SEQUOIA

The efficacy of BRUKINSA® in patients with previously untreated CLL/SLL was evaluated in a multicenter, open-label trial (SEQUOIA; NCT0333633). The trial required patients to be unsuitable for FCR therapy defined as either age ≥65 years or age 18 to <65 with a total Cumulative Illness Rating Scale (CIRS) >6, creatinine clearance 30 to 69 mL/min, or history of serious or recurrent infection. Patients without 17p deletion (17p del) were randomized to receive either BRUKINSA 160 mg twice daily until disease progression or unacceptable toxicity (n=241) or bendamustine plus rituximab (BR) for 6 cycles (n=238). Bendamustine was dosed at 90 mg/m2/day intravenously on the first 2 days of each cycle, and rituximab was dosed at 375 mg/m2 on day 1 of Cycle 1 and 500 mg/m2 on day 1 of Cycles 2 to 6 with a 28-day cycle length. Randomization was stratified by age, Binet stage, immunoglobulin variable region heavy chain (IGHV) mutational status, and geographic region.

Additionally, the same BRUKINSA regimen was evaluated in 110 patients with previously untreated, 17p del CLL/SLL in a non-randomized cohort.

Efficacy is summarized according to cohort.

Randomized cohort: previously untreated CLL/SLL without 17p deletion

In the randomized cohort of patients with previously untreated CLL/SLL without 17p deletion, the median age was 70 years; 62% were male, 89% were White, 3% were Asian, 1% were Black. Fifty-three percent of patients had an unmutated IGHV gene and 29% had Binet Stage C disease. Baseline characteristics were generally similar between treatment arms.

Efficacy in this cohort was based on progression-free survival as assessed by an IRC. Efficacy results are presented in Table 20 and Figure 1.

Table 20: Efficacy Results per IRC in Patients with Previously Untreated CLL/SLL without 17p Deletion in SEQUOIA (Randomized Cohort)

Parameter[a]	**CLL/SLL without del(17p)**	
	BRUKINSA (N=241)	**Bendamustine + Rituximab (N=238)**
Progression-free survival		
Number of Events, n	36 (15%)	71 (30%)
Disease Progression	27 (11%)	59 (25%)
Death	9 (3.7%)	12 (5%)
Median PFS (95% CI), months[b]	NE (NE, NE)	33.7 (28.1, NE)
HR (95% CI)[c]	0.42 (0.28, 0.63)	
P-value[d]	<0.0001	
Overall response rate[e]		
ORR, n (%)	225 (93)	203 (85)
95% CI, %	(89, 96)	(80, 90)
CR, n (%)	16 (7)	36 (15)
nPR, n (%)	3 (1.2)	14 (6)
PR, n (%)	206 (85)	153 (64)

CI=Confidence interval, CR=complete response, CRi=complete response with incomplete hematopoietic recovery, HR=hazard ratio, NE=not estimable, nPR=nodular partial response, ORR=overall response rate, PFS=progression-free survival, PR=partial response.

a Efficacy was assessed using the 2008 International Workshop for Chronic Lymphocytic Leukemia (iwCLL) guidelines and 2014 Lugano criteria for SLL.

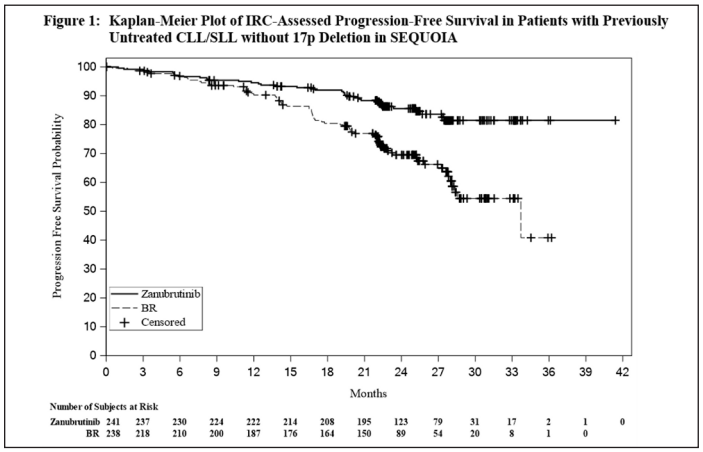
b Based on Kaplan-Meier estimation. Estimated median follow-up for PFS was 25.0 months.

c Based on a stratified Cox-regression model with bendamustine + rituximab as the reference group.

d Based on a stratified log-rank test, with a 2-sided significance level of 0.0372.

e Defined as CR, CRi, PR and nPR. No patients had CRi as best response.

Figure 1: Kaplan-Meier Plot of IRC-Assessed Progression-Free Survival in Patients with Previously Untreated CLL/SLL without 17p Deletion in SEQUOIA



At the time of analysis, overall survival data were immature. With an estimated median follow-up of 25.7 months, median overall survival was not reached in either arm, with fewer than 7% of patients experiencing an event.

Single-arm cohort: previously untreated CLL/SLL with 17p deletion

In this cohort, 110 patients with previously untreated CLL/SLL and centrally confirmed 17p deletion received BRUKINSA 160 mg twice daily until disease progression or unacceptable toxicity.

The median age was 70, 71% were male, 95% were White, and 1% were Asian. Sixty percent of patients had an unmutated IGHV gene and 35% had Binet Stage C disease.

Efficacy was based on overall response rate and duration of response as assessed by an IRC. Efficacy results are presented in Table 21.

Table 21: Efficacy Results Per IRC in Patients with Previously Untreated CLL/SLL and 17p Deletion in SEQUOIA

Parameter[a]	del(17p) CLL/SLL N=110
Overall response rate[b]	
ORR, n (%)	97 (88)
(95% CI, %)	(81, 94)
CR, n (%)	7 (6)
nPR, n (%)	2 (1.8)
PR, n (%)	88 (80)
Time to response	
Median (range), months	2.9 (1.9 to 13.9)
Duration of response	
Median DOR (95% CI),[c] months	NE (NE, NE)
Range, months	(5.6 to 35.9+)
Rate at 12 months, % (95% CI)[c]	96 (89, 98)
Rate at 18 months, % (95% CI)[c]	95 (88, 98)

DOR=duration of response. A + sign indicates a censored observation.

a Efficacy was assessed using the 2008 iwCLL guidelines and Lugano criteria for SLL.

b Defined as CR, CRi, PR and nPR. No patients had CRi as best response.

c Kaplan-Meier estimate. Estimated median follow-up for DOR was 25.1 months.

ALPINE

The efficacy of BRUKINSA in patients with relapsed or refractory CLL/SLL was evaluated in ALPINE, a randomized, multicenter, open-label, actively controlled trial (NCT03734016). The trial enrolled 652 patients with relapsed or refractory CLL/SLL after at least 1 systemic therapy. The patients were randomized in a 1:1 ratio to receive either BRUKINSA 160 mg orally twice daily (n=327) or ibrutinib 420 mg orally once daily (n=325), each administered until disease progression or unacceptable toxicity.

Randomization was stratified by age, geographic region, refractoriness to last therapy, and 17p deletion/TP53 mutation status.

Baseline characteristics were similar between treatment arms. Overall, the median age was 67 years, 68% were male, 81% were White, 14% were Asian, 1% were Black. Forty-three percent had advanced stage disease, 73% had an unmutated IGHV gene, and 23% had 17p deletion or TP53 mutation. Patients had a median of one prior line of therapy (range: 1-8), 18% of patients had ≥3 prior lines of therapy, 78% had prior chemoimmunotherapy, and 2.3% had prior BCL2 inhibitor.

Efficacy was based on overall response rate and duration of response as determined by an IRC. Efficacy results are shown in Table 22.

Table 22: Efficacy Results per IRC in Patients with Relapsed or Refractory CLL/SLL in ALPINE

Outcome[a]	Zanubrutinib (N=327)	Ibrutinib (N=325)
Overall response rate[b]		
ORR, n (%)	263 (80)	237 (73)
(95% CI, %)	(76, 85)	(68, 78)
CR, n (%)	13 (4.0)	8 (2.5)
nPR, n (%)	1 (0.3)	0 (0)
PR, n (%)	249 (76)	229 (70)
Response Rate Ratio (95% CI)[c]	1.10 (1.01, 1.20)	
2-sided p-value[d]	0.0264	
Time to response		
Median (range), months	5.5 (2.6 to 22.1)	5.6 (2.3 to 19.8)
Duration of response		
Median DOR (95% CI)[e]	NE (NE, NE)	NE (NE, NE)
Range, months	(1.4 to 30.4+)	(1.9+ to 30.8+)
Rate at 12 months, % (95% CI)[e]	92 (87, 95)	86 (80, 91)

CI=Confidence interval, CR=complete response, CRi=complete response with incomplete hematopoietic recovery, DOR=duration of response, HR=hazard ratio, NE=not estimable, nPR=nodular partial response, ORR=overall response rate, PR=partial response. A + sign indicates a censored observation.

a Efficacy was based on 2008 iwCLL guidelines for CLL and the Lugano criteria for SLL.

b Defined as CR + CRi + nPR + PR. No patients had CRi as best response.

c Estimate stratified by randomization stratification factors.

d 2-sided significance level of 0.0469 was allocated for ORR superiority testing.

e Based on Kaplan-Meier estimate. Estimated median follow-up for DOR was 14.1 months.

At the time of analysis, overall survival data were immature. With an estimated median follow-up of 24.7 months, median overall survival was not reached in either arm with 11% of patients experiencing an event.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Package Size	Content	NDC Number
120-count	Bottle with a child-resistant cap containing 120 capsules 80 mg, white to off-white opaque capsule, marked with "ZANU 80" in black ink	72579-011-02

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) *(see USP Controlled Room Temperature)*.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Hemorrhage

Inform patients to report signs or symptoms of severe bleeding. Inform patients that BRUKINSA may need to be interrupted for major surgeries or procedures [see Warnings and Precautions (5.1)].

Infections

Inform patients to report signs or symptoms suggestive of infection *[see Warnings and Precautions (5.2)]*.

Cytopenias

Inform patients that they will need periodic blood tests to check blood counts during treatment with BRUKINSA *[see Warnings and Precautions (5.3)]*.

Second Primary Malignancies

Inform patients that other malignancies have been reported in patients who have been treated with BRUKINSA, including skin cancer and other solid tumors. Advise patients to use sun protection and have monitoring for development of other cancers *[see Warnings and Precautions (5.4)]*.

Cardiac Arrhythmias

Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions (5.5)]*.

Embryo-Fetal Toxicity

Advise women of the potential hazard to a fetus and to use effective contraception during treatment and for 1 week after the last dose of BRUKINSA [see Warnings and Precautions (5.6)]. Advise males with female sexual partners of reproductive potential to use effective contraception during BRUKINSA treatment and for 1 week after the last dose of BRUKINSA *[see Use in Specific Populations (8.3)]*.

Lactation

Advise females not to breastfeed during treatment with BRUKINSA and for 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Administration Instructions

BRUKINSA may be taken with or without food. Advise patients that BRUKINSA capsules should be swallowed whole with a glass of water, without being opened, broken, or chewed *[see Dosage and Administration (2.1)]*.

Missed Dose

Advise patients that if they miss a dose of BRUKINSA, they may still take it as soon as possible on the same day with a return to the normal schedule the following day *[see Dosage and Administration (2.1)]*.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins, and herbal products *[see Drug Interactions (7.1)]*.

Manufactured for:
BeiGene USA, Inc.
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