BRUKINSA® (Zanubrutinib) Fact Sheet: ASCO 2022

About BRUKINSA®	BRUKINSA® is a small molecule inhibitor of Bruton's tyrosine kinase (BTK) that is currently being evaluated in a broad late-stage clinical trials program globally as a monotherapy and in combination with other therapies to treat various B cell malignancies.[i] To date, BRUKINSA is approved in more than 40 countries around the world, including China, European Union, Great Britain, Canada, Australia and South Korea in selected indications.[i]
Mechanism of Action	BTK is a key component of the B-cell receptor, or BCR, signaling pathway and is an important regulator of cell proliferation and cell survival in various B cell malignancies.[ii] When cancer forms in B-cells, they often have too much BTK, which causes the cancerous cells to grow.[iii] BRUKINSA is a BTK inhibitor that blocks BTK activity, which is associated with malignant B-cell growth and survival. Because new BTK is continuously synthesized, BRUKINSA was specifically designed to deliver complete and sustained inhibition of the BTK protein by optimizing bioavailability, half-life, and selectivity.[iv],[v] Due to its specificity and improved target occupancy, BRUKINSA may offer improved tolerability compared to first-generation BTK inhibitors, and reduced frequency of certain cardiovascular adverse events.[v]
BRUKINSA Clinical Development Program	BRUKINSA has been demonstrated to inhibit the proliferation of malignant B cells within a number of disease relevant tissues in studies.[vi] BeiGene's bold approach to clinical development—including two head-to-head trials [vii],[viii] —continues to generate evidence to support BRUKINSA's potential as a best-in-class BTK inhibitor. The global BRUKINSA development program includes approximately 4,000 subjects enrolled to-date in more than 25 countries and regions.
ASPEN Trial in R/R WM	The ASPEN Trial is a pivotal Phase 3 randomized, open-label, multicenter study evaluating BRUKINSA compared to ibrutinib in patients with relapsed/refractory or treatment-naïve Waldenström's macroglobulinemia (WM).[ix] ASPEN was the first randomized Phase 3 study comparing two BTK inhibitors in any indication and is the largest prospective randomized Phase 3 study in WM.[ix],[x] The ASPEN trial is a randomized Phase 3 trial in 229 patients with WM conducted in 61 centers in Europe, Australia, and the United States.[x] The study includes two cohorts, a randomized cohort (cohort 1) consisting of 201 patients with a MYD88 mutation and a non-randomized

	cohort (cohort 2) in which 28 patients with MYD88 wild-type ($MYD88^{WT}$) received zanubrutinib because they have historically responded poorly to ibrutinib therapy.[x]
	
	The randomized cohort 1 enrolled 102 patients (including 83 relapsed or refractory (R/R) patients and 19 treatment-naïve (TN) patients) in the zanubrutinib arm and 99 patients (including 81 R/R patients and 18 TN patients) in the ibrutinib arm.[x] Patients in the zanubrutinib arm were assigned to receive zanubrutinib 160 mg twice daily (BID) and patients in the ibrutinib arm received 420 mg of ibrutinib once daily (QD).[x]
	
	Results from cohort 1 in the Phase 3 ASPEN trial, as of the data cutoff date of August 31, 2019, with a median follow-up of 19.4 months, include[x]:
	• In the overall patient population, the VGPR rate as assessed by IRC was 28% in the zanubrutinib arm and 19% in the ibrutinib arm (no patients achieved a CR in either arm). The difference was not statistically significant (2-sided descriptive p=0.0921); In the R/R patient population, the major response rate (MRR), which is the rate of partial response (PR) or better, as assessed by IRC was 78% in the zanubrutinib arm and 80% in the ibrutinib arm; in the overall patient population, the MRR was 78% in the zanubrutinib arm and 78% in the ibrutinib arm[x];
	• In R/R patients, the VGPR rate as assessed by independent review committee (IRC) was 29% in the zanubrutinib arm and 20% in the ibrutinib arm (no patients achieved a CR in either arm). The difference was not statistically significant (2-sided p=0.1160)[x];
	• While the trial was not powered to detect a statistically significant improvement in progression free survival (PFS), and median PFS was not reached for either arm[x]:
	  • Event-free rates at 18 months were comparable: 86% in R/R patients and 85% in all patients in the zanubrutinib arm, compared to 82% in R/R patients and 84% in all patients in the ibrutinib arm; and
	  • The 18-month OS rate was 97% for all patients in the zanubrutinib arm, compared to 93% in all patients in the ibrutinib arm[x];
	• Grade ≥3 adverse events (AEs) were 58% in the zanubrutinib arm and 63% in the ibrutinib arm. In the zanubrutinib arm, four (4%) patients discontinued treatment due to AEs and there was one (1%) fatal adverse event; in the ibrutinib arm, nine patients (9%) discontinued due to AEs and there were four (4%) fatal adverse events[ix,x];
	• For AEs of special interest for BTK inhibitors, atrial fibrillation/flutter of any grade was 2% in the zanubrutinib arm and 15% in the ibrutinib arm; hemorrhage was 49% for zanubrutinib and 59% for ibrutinib; major hemorrhage was 6% for zanubrutinib and 9% for ibrutinib; and diarrhea was 21% for zanubrutinib and 32% for ibrutinib; and
	• The rate of neutropenia was higher in the zanubrutinib arm (30%) as compared to the ibrutinib arm (13%)[ix,x].

	At a median follow-up of 44 months, BRUKINSA continued to demonstrate clinically meaningful efficacy and a tolerable safety profile in patients with WM.[vii] • Exploratory analyses showed a consistent trend of deeper, earlier, and more durable responses (CR+VGPR) compared with ibrutinib over time [vii] • Median time to CR+VGPR was shorter for zanubrutinib: 6.7 months (range, 1.9-42.0) vs ibrutinib: 16.6 months (range, 2.0-49.9) [vii] • Over the follow-up period, patients receiving with zanubrutinib had fewer adverse events leading to death, treatment discontinuation, and dose reduction as compared with ibrutinib [vii] The prevalence of atrial fibrillation, hypertension, and bleeding were lower in the zanubrutinib arm at all time intervals; Neutropenia occurred early, and prevalence decreased over time for patients receiving zanubrutinib.[x] The ASPEN study consisted of a randomized comparison of zanubrutinib and ibrutinib efficacy and safety in patients with WM who have the *MYD88* mutation, as well as a separate cohort of patients without *MYD88* mutation (*MYD88*^{WT}) or with unknown mutational status who received zanubrutinib. Results from the latter single-arm cohort are reported herein. [xi] Efficacy endpoints included overall, major and complete (CR) or very good partial response (VGPR) rates, progression-free survival (PFS), duration of response (DOR), and overall survival (OS). [xi] Twenty-eight patients (23 relapsed/refractory; 5 treatment-naïve) were enrolled, including 26 with centrally confirmed *MYD88*^{WT} disease and 2 with unknown *MYD88* mutational status. At a median follow-up of 17.9 months, 7 of 26 *MYD88*^{WT} patients (27%) had achieved a VGPR and 50% a major response (partial response or better); there were no CRs. [xi] At 18 months, the estimated PFS and OS rates were 68% and 88%, respectively, while the median DOR had not been reached. Two patients discontinued zanubrutinib due to adverse events. Treatment-emergent hypertension, atrial fibrillation, and major hemorrhages were reported in 3, 1 and 2 patients (including 1 concurrent with enoxaparin therapy), respectively. Results of this substudy demonstrate that zanubrutinib monotherapy can induce high quality responses in patients with *MYD88*^{WT} WM.[xi]
ROSEWOOD Trial in Follicular Lymphoma *Investigational Study. BRUKINSA is not approved for FL*	ROSEWOOD is a randomized, open-label, Phase 2 study comparing BRUKINSA plus obinutuzumab to obinutuzumab alone in patients with R/R FL who have received two or more lines of therapy.[xii] The primary endpoint was overall response rate (ORR) assessed by independent central review (ICR) according to the Lugano classification.[xiii] A total of 217 patients were enrolled in the trial, with 145 patients receiving BRUKINSA plus obinutuzumab and 72 patients receiving obinutuzumab.[xiii] The ROSEWOOD trial met its primary endpoint with a 68.3% overall response rate (ORR) in the zanubrutinib plus obinutuzumab arm versus 45.8% in the obinutuzumab arm (p = 0.0017) and median follow-up of 12.5 months. Zanubrutinib plus obinutuzumab was generally well-

	tolerated, with safety results consistent with previous studies of both medicines.[xiii] • Zanubrutinib plus obinutuzumab was associated with a deep and durable response, with a complete response (CR) rate of 37.2% compared to 19.4% for obinutuzumab alone; 18-month duration of response rate was 70.9% in the zanubrutinib plus obinutuzumab arm versus 54.6% in the obinutuzumab arm[xiii] • Time to next anti-lymphoma treatment was significantly prolonged in the zanubrutinib plus obinutuzumab arm (HR 0.37; p <0.0001)[xiii] • Median progression-free survival was 27.4 months in the zanubrutinib plus obinutuzumab arm compared to 11.2 months in the obinutuzumab arm (HR: 0.51 [95% CI, 0.32 -0.81],)[xiii] • The most common any-grade and grade ≥ 3 toxicities in the zanubrutinib plus obinutuzumab arm were hematologic toxicities, and other toxicities were similar between the two arms[xiii] • Infusion-related reactions were more frequent in the obinutuzumab monotherapy arm[xiii]
SEQUOIA Trial *Investigational Study. Not approved for treatment -naive CLL/SLL*	The SEQUOIA trial is a randomized, global Phase 3 trial (NCT03336333) comparing BRUKINSA® (zanubrutinib) to bendamustine plus rituximab (B+R) in patients with treatment-naïve (TN) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).[xiv] **Study Design** SEQUOIA is a randomized, multicenter, global Phase 3 trial (NCT03336333) designed to evaluate the efficacy and safety of BRUKINSA compared to B+R in patients with TN CLL or SLL. The trial consists of three cohorts[xiv]: • Cohort 1 (n=479): randomized 1:1 to receive BRUKINSA (n=241) or B+R (n=238) until disease progression or unacceptable toxicity, in patients not harboring del(17p); data from this group comprise the primary endpoint[xiv] • Cohort 2 (n=110): patients with del(17p) receiving BRUKINSA as a monotherapy[xiv] • Cohort 3 (enrollment ongoing): patients with del(17p) or pathogenic TP53 variant receiving BRUKINSA in combination with venetoclax[xiv] Patients with del(17p) were not randomized to B+R, as they experience poor clinical outcomes and poor response to chemoimmunotherapy. The primary endpoint of the trial is IRC-assessed PFS. Secondary endpoints include investigator-assessed PFS, IRC- and investigator-assessed overall response rate (ORR), overall survival (OS), PFS and ORR in patients with del(17p), and safety. **Cohort 1: BRUKINSA vs. B+R in TN CLL Patients Without del (17p)[xiv]** At the interim analysis, with a median follow-up of 26.15 months, BRUKINSA demonstrated superiority in PFS over B+R, as assessed by IRC.[xiv] Results included: • The 24-month PFS rate was 85.5% (95% CI: 80.1, 89.6) in Arm A, compared to 69.5% (95% CI: 62.4, 75.5) in Arm B, with a hazard ratio (HR) of 0.42 (95% CI: 0.27, 0.63), $p < 0.0001$[xiv]

	• PFS benefit was consistently observed across key patient subgroups, including patients with del(11q), unmutated IGHV status, Binet stage C, and bulky disease [xiv]
	• Overall survival (OS) results were early, and at 24 months, OS probability was similar between two arms, with 94.3% (95% CI: 90.4, 96.7) in Arm A and 94.6% (95% CI: 90.6, 96.9) in Arm B [xiv]
	
	Safety analysis was based on 240 patients in Arm A and 227 patients in Arm B who received at least one dose of respective treatment. [xiv]
	
	BRUKINSA was generally well tolerated with a safety profile consistent with its broad clinical program, including a low rate of atrial fibrillation. The most common adverse events of any grade were consistent with the known safety profiles of each agent.[xiv]
	• 126 patients (52.5%) in Arm A experienced at least one Grade ≥3 AE, compared to 181 patients (79.7%) in Arm B, with the most common in both arms being neutropenia (11.3% in Arm A vs. 51.1% in Arm B) and thrombocytopenia (1.7% in Arm A vs. 7.0% in Arm B) [xiv]
	• 88 patients (36.7%) in Arm A experienced at least one serious AE, compared to 113 patients (49.8%) in Arm B [xiv]
	• AEs leading to dose reduction, interruption or delay, and discontinuation occurred in 18 patients (7.5%), 111 patients (46.3%), and 20 patients (8.3%), respectively, in Arm A, compared to 84 patients (37.4%), 154 patients (67.8%), and 31 patients (13.7%), respectively, in Arm B [xiv]
	• Fatal AEs were reported in 11 patients (4.6%) in Arm A, compared to 11 patients (4.8%) in Arm B [xiv]
	
	Cohort 2 (Arm C): BRUKINSA monotherapy in TN Patients with CLL/SLL with del(17p)[xv]
	• This cohort achieved significant efficacy with an 18-month PFS of 85%, as assessed by investigator.[x,xv]
	• With a median follow-up of 30.5 months, the 24-month PFS rate was 88.9% (95% CI: 81.3, 93.6). [xv]
	• Key safety findings included:
	  • 52.3% of patients experienced at least one Grade ≥3 AE, with the most common (in ≥2.0% of patients) being neutropenia/decreased neutrophil count, pneumonia, fall, and hypertension; [xv]
	  • 38.5% of the patients experienced at least one serious AE; and [xv]
	  • Five (4.6%) patients discontinued treatment due to AE, including two (1.8%) patients who experienced a fatal AE, one being pneumonia leading to sepsis and death, which was considered related to zanubrutinib, and the other being renal failure in the context of disease progression, which was considered unrelated to zanubrutinib. [xv]
	
	Cohort 3 (Arm D): BRUKINSA + Venetoclax in TN CLL Patients with del(17p) and/or TP53 Mutations[xvi]
	Cohort 3 is planned to enroll approximately 80 patients with TN CLL whose tumor exhibits del(17p) or TP53 mutations, with key endpoints

	being safety, overall response rate (ORR), PFS, and duration of response (DoR).[xvi] These patients will receive BRUKINSA treatment at 160 mg twice daily for three months, followed by combination treatment of BRUKINSA at the same dosing and venetoclax with a ramp-up dosing to 400 mg once daily for 12 to 24 cycles until progressive disease, unacceptable toxicity, or confirmed undetectable measurable residual disease (uMRD).[xvi] In Cohort 3, with a short median follow-up of 12.0 months, a high ORR was observed in the 36 patients who had at least one post-baseline response evaluation by the data cutoff date.[xvi] Preliminary efficacy results per investigator assessment included: • Of the 14 patients who received combination treatment for more than 12 months, five patients (36%) achieved a confirmed complete response (CR) or CR with incomplete bone marrow recovery (CRi) in a bone marrow assessment and four additional patients met the criteria for CR or CRi but not confirmed in bone marrow assessment due to COVID-19 restrictions; and[xvi] • In all 36 patients evaluable for efficacy, the ORR was 97.2% (95% CI: 85.5, 99.9) and the CR/CRi rate was 13.9% (all CRs or CRis were in patients who received combination treatment for more than 12 months).[xvi] • The most common adverse events of any grade were consistent with the known safety profiles of each agent.[xvi] With a median follow-up of 7.9 months, safety results in all 49 enrolled patients included: • 16 patients (32.7%) experienced at least one Grade ≥3 AE and four patients (8.2%) experienced at least one serious AE;[xvi] • AEs leading to dose interruption, dose reduction, and treatment discontinuation occurred in 10 patients (20.4%), no patients (0.0%), and one patient (2.0%), respectively; and[xvi] • One patient (2.0%) experienced a fatal AE.[xvi] With a median follow-up of 13.5 months, safety results in the 34 patients who received combination treatment included: • 13 patients (38.2%) experienced at least one Grade ≥3 AE and three patients (8.8%) experienced at least one serious AE; and[xvi] • AEs leading to dose interruption occurred in 10 patients (29.4%), with no AEs leading to dose reduction or treatment discontinuation.[xvi]
ALPINE Trial in R/R CLL or SLL *Investigational Study. BRUKINSA is not approved for CLL/SLL outside of China*	ALPINE is a randomized, global Phase 3 trial (NCT03734016) comparing BRUKINSA against ibrutinib in previously treated patients with relapsed or refractory chronic lymphocytic leukemia CLL or SLL.[xvii] In the trial, a total of 652 patients were randomized into two arms, with the first receiving BRUKINSA (160 mg orally twice daily) and the second receiving ibrutinib (420 mg orally once daily) until disease progression or unacceptable toxicity.[xvii] The primary analysis of ORR, defined by pre-specified non-inferiority of BRUKINSA versus ibrutinib, was assessed by investigator and IRC using the modified 2008 iwCLL guidelines, with modification for treatment-

	related lymphocytosis for patients with CLL, and per Lugano Classification for non-Hodgkin's lymphoma for patients with SLL. There was hierarchical testing of non-inferiority followed by superiority in ORR as assessed by investigator and IRC. [xvii] Key secondary endpoints include PFS and event rate of atrial fibrillation or flutter; other secondary endpoints include duration of response, overall survival, and incidence of adverse events. The study is ongoing with a planned formal analysis of PFS when the target number of events is reached. [xvii] Results from the planned interim analysis presented at the European Hematology Association Meeting in 2021[xvii] based on the first 415 patients enrolled in the ALPINE trial, including 207 on BRUKINSA treatment and 208 on ibrutinib treatment[xviii]. In the interim analysis, with a median follow-up time of 15.3 months, the trial met the primary endpoint with BRUKINSA demonstrating superiority in ORR, defined as the combined rate of complete responses (CRs) and partial responses (PRs), per investigator assessment. In the ORR analysis conducted by independent review committee (IRC), BRUKINSA demonstrated non-inferiority in the interim analysis. Efficacy results included [xviii]: • As assessed by investigator, BRUKINSA achieved an ORR of 78.3% (95% CI: 72.0, 83.7), a statistically significant improvement compared to 62.5% (95% CI: 55.5, 69.1) with ibrutinib (*p*=0.0006) [xviii]; • The ORR by independent review for zanubrutinib was 76.3% (95% CI, 69.9-81.9), which was non-inferior at a 1-sided p-value of <0.0001 to the ibrutinib ORR by independent review of 64.4% (95% CI, 57.5-70.9). Superiority was not demonstrated in the IRC analysis (p=0.0121, compared with the 2-sided statistical boundary of p<0.0099 set for the interim analysis). • In patients whose tumor exhibited chromosome 17p deletion (del[17p]), the ORR was 83.3% in the BRUKINSA arm, compared to 53.8% in the ibrutinib arm, as assessed by investigator [xviii]; • PFS data were early at the time of interim analysis and formal analysis will be performed when the target number of events is reached. The PFS rate at 12 months was 94.9% in the BRUKINSA arm, compared to 84.0% in the ibrutinib arm (descriptive *p*=0.0007; descriptive hazard ratio [HR]=0.40 [95% CI: 0.23, 0.69]), as assessed by investigator; and [xviii] • OS data were early at the time of interim analysis. The OS rate at 12 months was 97.0% in the BRUKINSA arm, compared to 92.7% in the ibrutinib arm (descriptive *p*=0.1081; descriptive HR=0.54 [95% CI: 0.25, 1.16]). [xviii] In the interim analysis, the ALPINE trial also met a pre-specified key secondary endpoint related to safety, with BRUKINSA demonstrating a statistically significant lower risk of atrial fibrillation or flutter and advantages in the overall cardiac safety profile, compared to ibrutinib. Treatment discontinuation was more common in the ibrutinib arm. [xvii]

	Safety results included: • 195 patients (95.6%) in the BRUKINSA arm experienced at least one adverse event (AE) of any grade, compared to 205 patients (99.0%) in the ibrutinib arm, and the most common (≥10%) AEs included anemia (BRUKINSA vs. ibrutinib: 13.2% vs. 15.0%), arthralgia (9.3% vs. 14.0%), contusion (10.3% vs. 8.7%), cough (12.7% vs. 6.3%), diarrhea (16.7% vs. 19.3%), hypertension (15.7% vs. 13.0%), muscle spasm (2.9% vs. 11.1%), neutropenia (19.6% vs. 15.5%), upper respiratory tract infection (21.6% vs. 14.0%), and urinary tract infection (10.8% vs. 8.2%); [xvii] • 114 patients (55.9%) in the BRUKINSA arm experienced Grade ≥3 AEs, compared to 106 patients (51.2%) in the ibrutinib arm; [xvii] • 56 patients (27.5%) in the BRUKINSA arm experienced serious AEs, compared to 67 patients (32.4%) in the ibrutinib arm; • Dose reduction and interruption due to AEs occurred in 23 patients (11.3%) and 81 patients (39.7%) in the BRUKINSA arm, respectively, compared to 25 patients (12.1%) and 84 patients (40.6%) in the ibrutinib arm; [xvii] • 16 patients (7.8%) discontinued BRUKINSA treatment due to AEs, with none caused by cardiac disorders; in comparison, 27 patients (13.0%) discontinued ibrutinib treatment due to AEs, with seven caused by cardiac disorders, including two of atrial fibrillation, and one each of cardiac arrest, cardiac failure, myocardial infarction, palpitations, and ventricular fibrillation; [xvii] • Fatal AEs were reported in eight patients (3.9%) in the BRUKINSA arm, compared to 12 patients (5.8%) in the ibrutinib arm; [xvii] • A key secondary endpoint of atrial fibrillation or flutter of any grade occurred in five patients (2.5%) in the BRUKINSA arm, significantly lower than the 21 patients (10.1%) in the ibrutinib arm (p=0.0014); [xvii] • Grade ≥3 atrial fibrillation or flutter occurred in two patients (1.0%) in the BRUKINSA arm, compared to four patients (1.9%) in the ibrutinib arm; [xvii] • Additional AEs of special interest of any grade included cardiac disorders (BRUKINSA vs. ibrutinib: 13.7% vs. 25.1%), hemorrhage (35.8% vs. 36.2%), major hemorrhage (2.9% vs. 3.9%), hypertension (16.7% vs. 16.4%), infections (59.8% vs. 63.3%), neutropenia (28.4% vs. 21.7%), secondary primary malignancies (8.3% vs. 6.3%), skin cancers (3.4% vs. 4.8%), and thrombocytopenia (9.3% vs. 12.6%); and [xvii] • Grade ≥3 AEs of special interest included cardiac disorders (BRUKINSA vs. ibrutinib: 2.5% vs. 6.8%), hemorrhage (2.9% vs. 2.9%), major hemorrhage (2.9% vs. 2.9%), hypertension (10.8% vs. 10.6%), infections (12.7% vs. 17.9%), neutropenia (18.6% vs. 15.0%), secondary primary malignancies (4.9% vs. 1.9%), skin cancers (1.5% vs. 1.0%), and thrombocytopenia (3.4% vs. 3.4%). [xvii]
Important Safety Information & Indications	**<u>IMPORTANT SAFETY INFORMATION</u>** **<u>Warnings and Precautions</u>**

	Hemorrhage Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 3.4% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade occurred in 35% of patients treated with BRUKINSA monotherapy. Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration 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. **Infections** Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 27% of patients, most commonly pneumonia. 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. **Cytopenias** Grade 3 or 4 cytopenias, including neutropenia (26%), thrombocytopenia (11%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 3.6% of patients. 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. **Second Primary Malignancies** Second primary malignancies, including non-skin carcinoma, have occurred in 14% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer, reported in 8% of patients. Other second primary malignancies included malignant solid tumors (4.0%), melanoma (1.7%) and hematologic malignancies (1.2%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

	Cardiac Arrhythmias Atrial fibrillation and atrial flutter were reported in 3.2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 1.1% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate. **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** The most common adverse reactions, including laboratory abnormalities, in ≥ 30% of patients who received BRUKINSA (N = 847) included decreased neutrophil count (54%), upper respiratory tract infection (47%), decreased platelet count (41%), hemorrhage (35%), decreased lymphocyte count (31%), rash (31%) and musculoskeletal pain (30%). **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 moderate or strong CYP3A inducers. **Specific Populations** 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 mantle cell lymphoma (MCL) who have received at least one prior therapy. 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. • BRUKINSA is indicated for the treatment of adult patients with

	Waldenström's macroglobulinemia (WM). • 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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. **Please see full Prescribing Information including Patient Information.**

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