Physician's Prescribing Information

1. Name of the Medicinal Product

BRUKINSA

2. Qualitative and Quantitative Composition

Each capsule contains 80 mg Zanubrutinib
For full list of excipients, see section 6.1

3. Pharmaceutical Form

Capsules

4. Therapeutic Indication

BRUKINSA is indicated for: the treatment of adult patients with

- Mantle cell lymphoma (MCL) who have received at least one prior therapy.
- Waldenström's macroglobulinemia (WM).
- Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti- CD20-based regimen.Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
- Relapsed or refractory follicular lymphoma (FL), in combination with obinutuzumab, after two or more lines of systemic therapy.

5. DOSAGE AND ADMINISTRATION

5.1 Recommended Dosage

The recommended dosage of BRUKINSA for monotherapy or in combination with obinutuzumab 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.

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BRUKINSA in combination with obinutuzumab BRUKINSA should be administered orally before obinutuzumab infusion. The recommended dose is obinutuzumab 1,000 mg intravenously on Days 1, 8, and 15 of Cycle 1, and on Day 1 of every 28-day cycle from Cycles 2 to 6. At the discretion of the physician, obinutuzumab may be administered 100 mg on Day 1 and 900 mg on Day 2 of Cycle 1 instead of 1,000 mg on Day 1 of Cycle 1. Obinutuzumab maintenance (one infusion every two months for up to two years) may be prescribed. Refer to the obinutuzumab SPC for additional dosing information, including premedication before each infusion.

5.2 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 (11.7) and Clinical Pharmacology (13.3)]*.

5.3 Dosage Modifications for Drug Interactions

Recommended dosage modifications of BRUKINSA for drug interactions are provided in Table 1 *[see Drug Interactions (10.1)]*.

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

Coadministered Drug	**Recommended BRUKINSA Dosage**
Strong CYP3A inhibitor	80 mg once daily Interrupt dose as recommended for adverse reactions ***[see Dosage and Administration (5.4)].***
Strong CYP3A inhibitor	80 mg once daily Interrupt dose as recommended for adverse reactions *[see Dosage and Administration (5.4)].*
Moderate CYP3A inhibitor	80 mg twice daily Modify dose as recommended for adverse reactions *[see Dosage and Administration (5.4)].*
Moderate or strongCYP3A inducer	Avoid concomitant use.

After discontinuation of a CYP3A inhibitor , resume previous dose of BRUKINSA *[see Dosage and Administration (5.1, 5.2) and Drug Interactions (10.1)]*.

5.4 Dosage Modifications for Adverse Reactions

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

Table 2: **Recommended Dosage Modifications 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 (8.3)]*		
Grade 3 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

Grade 3 thrombocytopenia with significant bleeding Grade 4 neutropenia(lasting more than 10 consecutive days) Grade 4 thrombocytopenia (lasting more than 10 consecutive days)	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
Non-hematological toxicities *[see Warnings and Precautions (8.5) and Adverse Reactions (9.1)]*		
Grade 3 or 4 non-hematological toxicities *	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^
	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

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

Asymptomatic lymphocytosis in CLL and MCL should not be regarded as an adverse reaction, and these patients should continue taking BRUKINSA.
Refer to the obinutuzumab prescribing information for management of obinutuzumab toxicities.

6. 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.

6.1. List of Excipients: Microcrystalline cellulose, Croscarmellose sodium, Sodium lauryl sulphate, Colloidal silicon dioxide, Magnesium stearate
Capsule Shell : Gelatin ,Titanium Dioxide. Imprinting Ink(traces)

7. CONTRAINDICATIONS

None.

8. WARNINGS AND PRECAUTIONS

8.1 Hemorrhage

Fatal and serious hemorrage has occurred in patients with hematological malignancies treated with BRUKINSA. Grade 3 or higher hemorrhage including intracranial andgastrointestinal hemorrhage,

hematuria ,and hemothorax was reported in 3.8% of patients treated with BRUKINSA. ,in clinical trials , with fatalities occurring in 0.2% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 32% 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 before and after surgery depending upon the type of surgery and the risk of bleeding.

8.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA. Grade 3 or higher infections occurred in 26% of patients, most commonly pneumonia. (7.9%), with fatal infections occurring in 3.2% 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.

8.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (21%), thrombocytopenia (8%) and anemia (8%) based on laboratory measurements, developed in patients treated with BRUKINSA *[see Adverse Reactions (9.1)]*. Grade 4 neutropenia occurred in 10% of patients, and Grade 4 thrombocytopenia occurred in 2.5% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dosage and Administration (5.4)]*. Treat using growth factor or transfusions, as needed.

8.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 14% of patients treated with BRUKINSA. The most frequent second primary malignancy was non-melanoma skin cancers (8%) followed by other solid tumors in 7% of the patients (including melanoma in 1% of patients) and hematologic malignancies (0.7%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

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8.5 Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 4.4% of patients treated with BRUKINSA including Grade 3 or higher cases in 1. 9% 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 0.3% of patients. Monitor for signs and symptoms of cardiac arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately *[see Dosage and Administration (5.4)]*, and consider the risks and benefits of continued BRUKINSA treatment.

8.6 Hepatotoxicity, Including Drug-Induced Liver Injury

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI), has occurred in patients treated with Bruton tyrosine kinase inhibitors, including BRUKINSA.

Evaluate bilirubin and transaminases at baseline and throughout treatment with BRUKINSA. For patients who develop abnormal liver tests after BRUKINSA, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold BRUKINSA. Upon confirmation of DILI, discontinue BRUKINSA.

8.7 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 (11.1)]*.

9 ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions (8.1)]*
- Infections *[see Warnings and Precautions (8.2)]*
- Cytopenias *[see Warnings and Precautions (8.3)]*
- Second Primary Malignancies *[see Warnings and Precautions (8.4)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (8.5)]*

9.1 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 in nine monotherapy and 2 combination clinical trials, administered at 160 mg twice daily in 1608 patients and at 320 mg once daily in 121 patients. Among these 1729 patients, the median duration of exposure was27.6 months, 78% of patients were exposed for at least 12 months, and 60% of patients were exposed for at least 24 months.

In this pooled safety population, the most common adverse reactions (≥30%), including laboratory abnormalities, iwere neutrophil count decreased (51%), platelet count decreased (41%) upper respiratory tract infection (38%), hemorrhage (32%), and musculoskeletal pain (31%).

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 (15.1)]*. 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 x 10^9/L and an absolute neutrophil count ≥ 1 x 10^9/L independent of growth factor support, hepatic enzymes ≤ 2.5 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. The BGB-3111-AU-003 trial required a platelet count ≥ 50 x 10^9/L and an absolute neutrophil count ≥ 1 x 10^9/L independent of

growth factor support, hepatic enzymes
≤ 3 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. Both trials required a Creatinine clearance (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 adverse reactions 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	.4[c]
	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

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[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 (*MYD88^{MUT}*) 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 (*MYD88^{WT}*) WM patients and 2 patients with unknown MYD88 status *[see Clinical Studies (15.2)]*.

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 reaction leading to dose reduction occurred in 2 patients in Cohort 2 (each with one event: diarrhea and pneumonia).

Table 5summarizes 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	2.0	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 (15.3)]*.The trials required an absolute neutrophil count ≥ 1 x 10^9/L, platelet count ≥ 50 or ≥ 75 x 10^9/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 White 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 treatmentfor 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 infections [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 trials 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, CLcr 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/m^2/day intravenously on the first 2 days of each cycle, and rituximab was dosed at 375 mg/m^2 on day 1 of Cycle 1 and 500 mg/m^2 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

	CLL/SLL without 17p deletion			
	BRUKINSA (N=240)		**BR (N=227)**	
System Organ Class Preferred Term	**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] Nonfasting 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
Pneumonia[b]	20*	8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[c]	38	2.7
Skin and subcutaneous tissue disorders		
Rash[d]	28	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
Constipation	15	0
Abdominal pain[g]	12	1.8
Respiratory, thoracic and mediastinal disorders		
Cough[g]	18	0
Dyspnea[g]	13	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	14	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
Nervous system disorders				
Dizziness[f]	10	0.0	7	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	23	0
Phosphate decreased	21	2.5	13	2.2
Calcium decreased	21	0.6	29	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.

Follicular Lymphoma

The safety of BRUKINSA in combination with obinutuzumab was evaluated in 143 adult patients with relapsed or refractory follicular lymphoma (FL) in study BGB-3111-212 (ROSEWOOD), a randomized, multicenter, open-label trial *[see Clinical Studies (14.5)]*. The trial required an absolute neutrophil count ≥1 × 10^9/L, platelet count ≥50 × 10^9/L, and CLcr ≥30 mL/min and excluded patients requiring a strong CYP3A inhibitor or inducer.

Patients were randomized to receive either BRUKINSA 160 mg twice daily until disease progression or unacceptable toxicity plus obinutuzumab (n=143) or obinutuzumab monotherapy (n=71). Obinutuzumab was dosed at 1,000 mg intravenously on Days 1, 8, and 15 of Cycle 1; on Day 1 of Cycles 2 to 6; and then every 8 weeks for up to 20 doses. At the discretion of the investigator, obinutuzumab was administered intravenously on Day 1 (100 mg) and on Day 2 (900 mg) of Cycle 1 instead of 1,000 mg on Day 1 of Cycle 1.

In patients who received BRUKINSA in combination with obinutuzumab, the median age was 63, 49% were female, 63% were White, and 21% were Asian. Most patients (97%) had an ECOG performance status of 0 to 1. The median duration of BRUKINSA treatment was 12 months, with 24% of patients treated for at least 2 years.

Serious adverse reactions occurred in 35% of patients who received BRUKINSA in combination with obinutuzumab. Serious adverse reactions in ≥5% of patients included pneumonia (11%) and COVID-19 (10%). Fatal adverse reactions occurred in 4.2% of patients, with the leading cause of death being COVID-19 (2.1%).

Adverse reactions led to permanent discontinuation of BRUKINSA in 17% of patients, dose reduction in 9%, and dose interruption in 40%. Adverse reactions leading to permanent discontinuation in ≥2% of patients were pneumonia, COVID-19, and second primary malignancy. The leading causes of BRUKINSA dosage modification (42% of all patients) were pneumonia, COVID-19, thrombocytopenia, and neutropenia.

Table 15 summarizes adverse reactions in BGB-3111-212.

Table 15: Adverse Reactions in ≥10% of Patients with Relapsed or Refractory FL Who Received BRUKINSA in Study BGB-3111-212

System Organ Class Preferred Term	BGB-3111-212			
	BRUKINSA + Obinutuzumab (N=143)		Obinutuzumab (N=71)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions				
Fatigue[a,b]	27	1.4	25	1.4
Pyrexia	13	0	20	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[a,c]	22	3.5	23	1.4
Vascular disorders				
Hemorrhage[a,d]	20	1.4	10	1.4
Gastrointestinal disorders				
Diarrhea	18	2.8	17	1.4
Constipation	13	0	9	0
Abdominal pain[a]	11	2.1	11	0
Infections and infestations				
Upper respiratory tract infection[a,e]	17	2.8	10	0
Pneumonia[a,f,*]	15	13	11	7
COVID-19[a,*]	13	9	11	4.2
Herpes virus infection[g]	11	2.1	1.4	0
Urinary tract infection[h]	10	1.4	7	0
Respiratory, thoracic, and mediastinal disorders				
Cough[a]	14	0	14	0
Dyspnea[a,*]	11	2.1	13	0
Skin and subcutaneous tissue disorders				
Rash[a,i]	11	0	14	0

***** Includes fatal outcomes: COVID-19 (3 patients), pneumonia (2 patients), dyspnea (1 patient).

[a] Includes multiple related terms.

[b] Fatigue: Fatigue, asthenia, and lethargy.

[c] Musculoskeletal pain: Back pain, musculoskeletal pain, musculoskeletal discomfort, noncardiac chest pain, neck pain, pain in extremity, myalgia, spinal pain, bone pain, arthralgia, and related terms.

[d] Hemorrhage: All terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.

[e] Upper respiratory tract infection: Upper respiratory tract infection, sinusitis, pharyngitis, laryngitis, rhinitis, nasopharyngitis, laryngopharyngitis, tonsillitis bacterial, and related terms.

[f] Pneumonia: Pneumonia, COVID-19 pneumonia, lung infiltration, lung consolidation, and related terms including specific types of infection.

[g] Herpes virus infection: Herpes viral infection, herpes zoster, herpes simplex, herpes simplex reactivation, varicella, and Epstein-Barr viremia.

[h] Urinary tract infection: Urinary tract infection, cystitis, pyelonephritis, and related terms.

[i] Rash: Rash, erythema, dermatitis, drug eruption, skin reaction, and related terms.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA in combination with obinutuzumab included bruising, edema, pruritus, petechiae, vomiting, headache, arthralgia, hypertension, sepsis, cardiac arrhythmias, renal insufficiency, febrile neutropenia, transaminase elevation, and pneumonitis.

Table 16: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients Who Received BRUKINSA in Study BGB-3111-212

Laboratory Abnormality[a]	BGB-3111-212			
	BRUKINSA + Obinutuzumab		Obinutuzumab	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Platelets decreased	65	11	43	11
Neutrophils decreased	47	17	42	14
Hemoglobin decreased	31	0.8	23	0
Lymphocytes decreased	30	11	51	25
Chemistry				
Glucose increased[b]	53	8	41	9
Alanine aminotransferase increased	23	0	28	0
Phosphate decreased	21	0.8	14	0

[a] The denominator used to calculate the rate was 122 in the BRUKINSA + obinutuzumab arm, and varied from 56 to 58 in the obinutuzumab 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] Nonfasting conditions.

9.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of BRUKINSA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. • Hepatobiliary disorder: drug-induced liver injury

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

10 DRUG INTERACTIONS

10.1 Effect of Other Drugs on BRUKINSA

Table 17: 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 (13.3)]* 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 (5.3)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Coadministration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (13.3)]* which may reduce BRUKINSA efficacy.
Prevention or management	• Avoid coadministration of BRUKINSA with strong or moderate CYP3A inducers *[see Dosage and Administration (5.3)]*.

11 USE IN SPECIFIC POPULATIONS

11.1 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 postimplantation 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.

11.2 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.

11.3 Females and Males of Reproductive Potential

BRUKINSA can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (11.1)]*.

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.

11.4 Pediatric Use

Safety and effectiveness of BRUKINSA in pediatric patients have not been established.

11.5 Geriatric Use

Of the 1729 patients with MCL, MZL, WM, CLL/SLL, and FL in clinical studies with BRUKINSA, 59% were ≥65 years of age, and 21% 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 (57% and 38%, respectively) than patients <65 years of age (51% and 29%, respectively). No overall differences in effectiveness were observed between younger and older patients.

11.6 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 (13.3)]*.

11.7 Hepatic Impairment

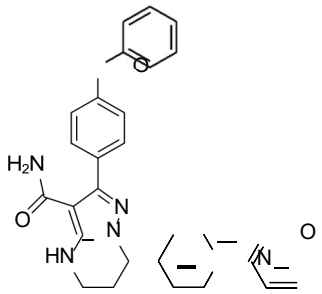
Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment *[see Dosage and Administration (5.2)]*. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment *[see Clinical Pharmacology (13.3)]*.

12 DESCRIPTION

BRUKINSA (zanubrutinib) is a kinase inhibitor. The empirical formula of zanubrutinib is $C_{27}H_{29}N_5O_3$ 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.

13 CLINICAL PHARMACOLOGY

13.1 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.

13.2 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.

In Vitro Platelet Aggregation

In blood samples from healthy donors, patients on anticoagulant or antiplatelet therapy, and those with severe renal dysfunction, zanubrutinib demonstrated inhibition of platelet aggregation mediated by collagen, CRP-XL, or rhodocytin. Zanubrutinib did not show meaningful inhibition of platelet aggregation for ADP and PAR4-AP.

13.3 Pharmacokinetics

Zanubrutinib maximum plasma concentration (C_{max}) 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 C_{max} is 295 (55%) ng/mL following 160 mg twice daily and 537 (55%) ng/mL following 320 mg once daily.

Absorption

The median t_{max} of zanubrutinib is 2 hours.

Effect of Food

No clinically significant differences in zanubrutinib AUC or C_{max} were observed following 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 ($t_{½}$) 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 zanubrutinibis 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, White, and Other), body weight (36 to 144 kg), or mild, moderate, or severe renal impairment 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 C_{max} and AUC (Table 18).

Table 18: Observed or Predicted Increase in Zanubrutinib Exposure After Co-Administration of CYP3A Inhibitors

Coadministered CYP3A Inhibitor	**Increase in Zanubrutinib C_{max}**	**Increase in Zanubrutinib AUC**
	Observed	
Itraconazole (200 mg once daily)[a]	157%	278%
Fluconazole (400 mg once daily)[b]	81%	88%
Diltiazem (180 mg once daily)[b]	62%	62%
Voriconazole (200 mg twice daily)[b]	229%	230%
Clarithromycin (250 mg twice daily)[b]	101%	92%
	Predicted	
Posaconazole suspension (100 mg once daily)[c]	169%	180%
Posaconazole suspension (100 mg twice daily)[c]	207%	279%
Posaconazole delayed-release tablets (300 mg once daily)[c]	232%	407%
Posaconazole intravenously (300 mg once daily)[c]	205%	333%
Itraconazole (200 mg once daily)[c]	273%	320%

[a] The assessment was conducted in healthy subjects with a single dose of zanubrutinib 20 mg.
[b] The assessment was conducted in patients with B-cell lymphoma administered multiple doses of zanubrutinib at the respective recommended zanubrutinib dosages in Table 1.
[c] The predicted values were based on simulations with patients administered multiple doses of zanubrutinib at the respective recommended dosages in Table 1.

CYP3A Inducers: Coadministration of multiple doses of rifampin (strong CYP3A inducer) decreased the zanubrutinib C_{max} 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 C_{max} by 58% and AUC by 60%.

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

CYP2C19 Substrates: Coadministration of multiple doses of zanubrutinib decreased omeprazole (CYP2C19 substrate) C_{max} 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) C_{max} 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.

14 NONCLINICAL TOXICOLOGY

14.1 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 at lower doses ,but at the highest dose tested, morphological abnormalities in sperm and increased postimplantation loss were noted. The high dose of 300 mg/kg/day is approximately 10 times the human recommended dose, based on body surface area.

15 CLINICAL STUDIES

15.1 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 White (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 (IRC).

Table 19: Efficacy Results per IRC in Patients with MCL

	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

15.2 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 (MYD88MUT) 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 vs1-3 vs > 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 pre-specified efficacy outcome of superior CR+VGPR as assessed by IRC, tested first in patients with R/R disease in ASPEN.

Table 20 shows the response rates in ASPEN based on IRC assessment.

Table 20 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 (N=99)	BRUKINSA (N=102)	Ibrutinib (N=99)
Response rate (CR+VGPR+PR), (%)	79 (77.5)	77 (77.8)	79 (77.5)	77 (77.8)
95% CI (%)[a]	(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)
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)	58 (58.6)
Duration of response (DOR), Event-free at 12 months (95% CI)[b]	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). Eighty- six percent 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).

15.3 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 21).

Table 21 **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 Rate at 12	NE (NE, NE)85%	NE (8.4, NE)
months (95% CI)	(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%.

15.4 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; NCT03336333). 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/m^2/day intravenously on the first 2 days of each cycle, and rituximab was dosed at 375 mg/m^2 on day 1 of Cycle 1 and 500 mg/m^2 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, and 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 Table22 and Figure 1.

Table 22: 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.

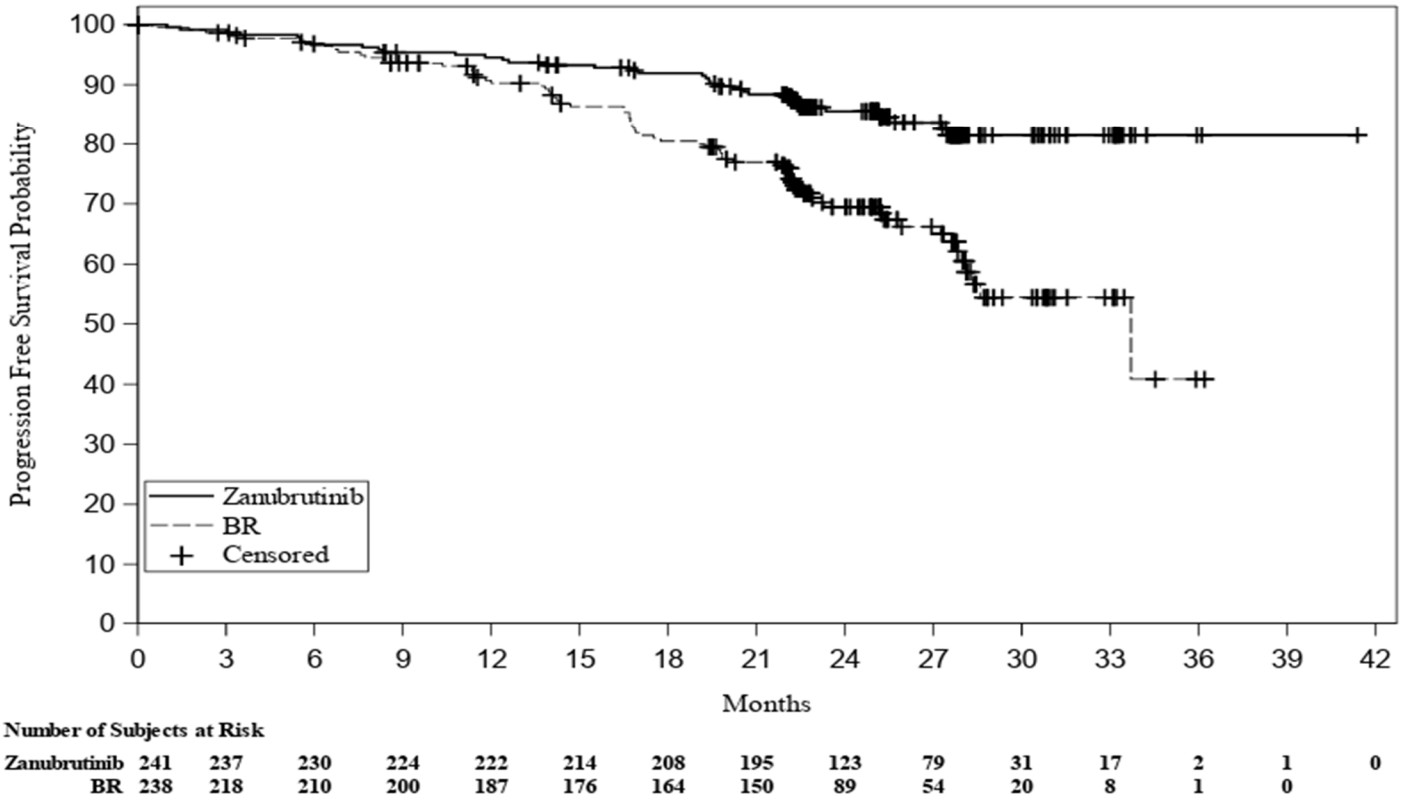
[b] Based on Kaplan-Meier estimation. Estimated median follow-up for PFS was 25 months.

[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 23

Table 23: 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. For pregression-free survival per IRC, the final analysis occurred with a median follow-up of 31 months

.Efficacy results are shown in Table 24 and Figure 2

Table 24: Efficacy Results per IRC in Patients with Relapsed or Refractory CLL/SLL in ALPINE

Parameter [a]	**BRUKINSA (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	
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)
Progression-free survival		
Events, n (%)	88 (27)	120 (37)
Median PFS (95% CI), months[f]	NE (34.3, NE)	35 (33.2, 44.3)
HR (95% CI)[g]	0.65 (0.49, 0.86)	
2-sided p-value[h]	0.0024	

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.

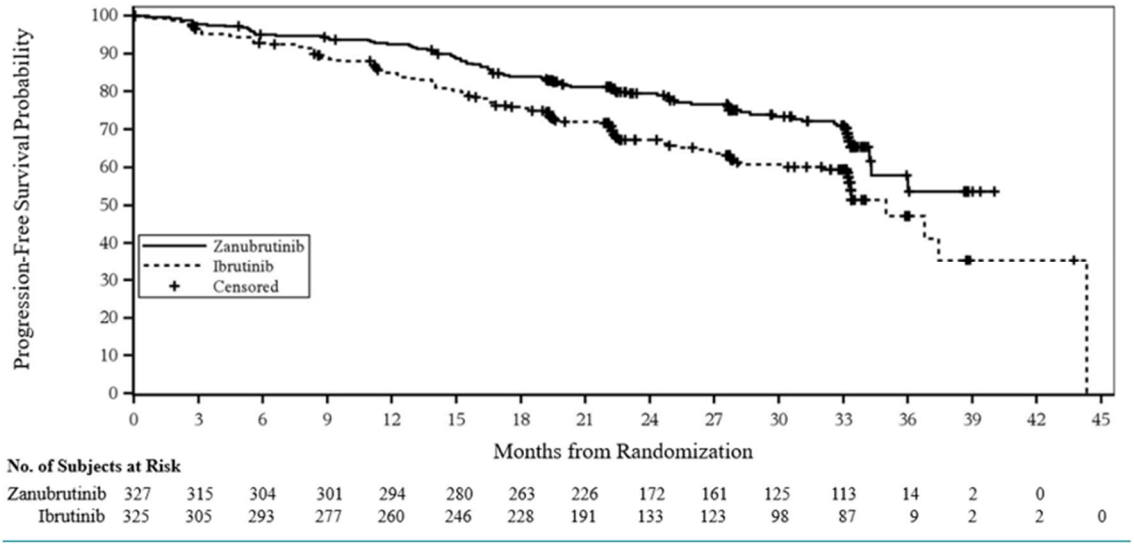
[f]Based on Kaplan-Meier estimation. Estimated median follow-up for PFS was 30.7 months, median overall survival was not reached in either arm with 11% of patients experiencing an event.

[g] Based on a stratified Cox-regression model with ibrutinib as the reference group.

[h] Based on a stratified log rank test.

The median time to response was 5.5 months for BRUKINSA and 5.6 months for ibrutinib.

Figure 2: Kaplan-Meier Plot of Progression-Free Survival by IRC in ALPINE



At the time of final analysis, the median overall survival was not reached in either arm. There were a total of 108 deaths: 48 (14.7%) in the zanubrutinib arm and 60 (18.5%) in the ibrutinib arm.

15.5 Follicular Lymphoma

The efficacy of BRUKINSA, in combination with obinutuzumab, was evaluated in Study BGB-3111-212 (ROSEWOOD; NCT03332017), an open-label, multicenter, randomized trial that enrolled 217 adult patients with relapsed or refractory FL after at least 2 prior systemic treatments. The study required prior receipt of an anti-CD20 antibody and an alkylator-based combination therapy, and excluded patients with FL Grade 3b, transformed lymphoma, and prior exposure to a BTK inhibitor.

Patients were randomized in a 2:1 ratio to receive either BRUKINSA 160 mg orally twice daily until disease

progression or unacceptable toxicity plus obinutuzumab, or obinutuzumab alone. Obinutuzumab was administered 1,000 mg intravenously on days 1, 8, and 15 of Cycle 1, 1,000 mg on Day 1 of Cycles 2 to 6; and then 1,000 mg every 8 weeks for up to 20 doses. At the discretion of the investigator, obinutuzumab could be administered as 100 mg on Day 1 and 900 mg on Day 2 of Cycle 1.

Randomization was stratified by the number of prior lines of therapy (2 to 3 vs >3), rituximab-refractory status (yes vs no), and geographic region.

Of the 217 patients randomized (145 to BRUKINSA plus obinutuzumab, 72 to obinutuzumab monotherapy), the median age was 64 years (range: 31 to 88), 50% were male, 64% were White, and 22% were Asian. In total, 83% had stage 3 or 4 disease and 57% met Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria at enrollment. Patients had a median of 3 prior lines of therapy (range: 2-11), with 27% of patients having more than 3 prior lines of therapy.

In the BRUKINSA in combination with obinutuzumab arm, 5% had received lenalidomide plus rituximab, 21% had received stem cell transplantation, 53% had refractory disease to rituximab, and 37% had progression of disease within 24 months of the first systemic therapy.

Efficacy was based on overall response rate and duration of response, as determined by an IRC. Efficacy results are shown in Table 25. The median time to response in the BRUKINSA combination arm was 2.8 months (range 2 to 23 months).

Table 25: Efficacy Results per IRC in Patients with Relapsed or Refractory Follicular Lymphoma

Parameter	**BRUKINSA + Obinutuzumab (N=145)**	**Obinutuzumab (N=72)**
Overall response rate		
ORR, n (%)	100 (69)	33 (46)
(95% CI)[a]	(61, 76)	(34, 58)
CR	57 (39)	14 (19)
PR	43 (30)	19 (26)
Risk difference, % (95% CI)[b]	22.7 (9, 36.5)	
2-sided p-value[b,c]	0.0012	
Duration of response		
Median DOR (95% CI),[d] months	NE (25.3, NE)	14 (9.2, 25.1)

CI=Confidence interval, CR=complete response, DOR=duration of response, NE=not estimable, ORR=overall response rate, PR=partial response.

[a] Estimated using the Clopper-Pearson method.

[b] Estimated by stratified Cochran-Mantel-Haenszel method.

[c] Significance level, 0.05.

[d] Estimated by Kaplan-Meier method. Estimated median follow-up for DOR was 19 months overall.

The estimated DOR rate at 18 months was 69% (95% CI: 58, 78) in the BRUKINSA combination arm and 42% (95% CI: 23, 60) in the obinutuzumab monotherapy arm.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Package Size	**Content**
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

Storage

Store below 25°C

Shelf life

The expiry date of the product is indicated on the packaging materials.

17. MANUFACTURER

BeiGene USA,
Inc.
San Mateo, CA
94404

18. LICENSE HOLDER

Medison Pharma Ltd.
10 Hashiloach St., POB 7090 Petach Tikva

19. REGISTRATION NUMBER

166-56-36452-99

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