

# THE BTK INHIBITOR THAT DELIVERS POWERFUL AND SUSTAINED RESPONSES<sup>1,2</sup>

BRUKINSA® (zanubrutinib) is a kinase inhibitor indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

## The first and only head-to-head trial of BTK inhibitors in WM

A global, randomized Phase 3 trial in WM across a broad range of patients<sup>1</sup>

- Treatment-naïve
- MYD88<sup>MUT</sup> (CXCR4<sup>WT</sup>, CXCR4<sup>WHIM</sup>)
- Relapsed/refractory
- MYD88<sup>WT</sup>

\*Patients were enrolled from the United States, Europe, and Australia/New Zealand.



24-hour inhibition of BTK was maintained at 100% in peripheral blood mononuclear cells (PBMCs) and 94% to 100% in lymph nodes when taken at the recommended total daily dose of 320 mg. The clinical significance of 100% inhibition has not been established.<sup>1,2</sup>

## Powerful Responses With BRUKINSA Across All WM Patients

All patients <sup>1</sup> IWWM-6 criteria <sup>1</sup> (Cohort 1)			All patients <sup>1</sup> Modified IWWM-6 criteria <sup>1</sup> (Cohort 1)		
BRUKINSA (N=102)			BRUKINSA (N=102)		
78% CR+VGPR+PR (95% CI: 68, 85)	16% VGPR/CR <sup>1</sup>	62% PR	78% CR+VGPR+PR (95% CI: 68, 85)	28% VGPR/CR <sup>1</sup>	49% PR
Ibrutinib (N=99)			Ibrutinib (N=99)		
78% CR+VGPR+PR (95% CI: 68, 86)	7% VGPR/CR	71% PR	78% CR+VGPR+PR (95% CI: 68, 86)	19% VGPR/CR	59% PR

While the primary endpoint of superiority did not reach statistical significance, numerically higher VGPR/CR rates were achieved in the BRUKINSA treatment arm.<sup>1</sup>

- Median follow-up time was 19.4 months<sup>3</sup>
- The prespecified efficacy outcome measure of VGPR/CR was assessed by IRC<sup>1</sup>

## Consistent Responses With BRUKINSA Regardless of Line of Therapy or Mutation

### Cohort 1: Response by line of therapy (modified IWWM-6 criteria)<sup>3</sup> (Exploratory subgroup analysis)

Treatment-naïve	BRUKINSA (n=19)	Ibrutinib (n=18)
ORR	95% (95% CI: 74, 100)	89% (95% CI: 65, 99)
VGPR/CR	26%	17%
PR	47%	50%

  

Relapsed/refractory	BRUKINSA (n=83)	Ibrutinib (n=81)
ORR	94% (95% CI: 87, 98)	94% (95% CI: 86, 98)
VGPR/CR	29%	20%
PR	49%	61%

### Cohort 1: Response by mutation (modified IWWM-6 criteria)<sup>3,5</sup> (Exploratory subgroup analysis)

CXCR4 <sup>WT</sup>	BRUKINSA (n=65)	Ibrutinib (n=72)
CR+VGPR+PR	82%	82%
VGPR/CR	34%	24%
PR	48%	58%

  

CXCR4 <sup>WHIM</sup>	BRUKINSA (n=33)	Ibrutinib (n=20)
CR+VGPR+PR	70%	65%
VGPR/CR	18%	10%
PR	52%	55%

The median follow-up time was 19.4 months for Cohort 1 and 17.9 months for Cohort 2.<sup>3,4</sup>

All subgroup analyses are exploratory and descriptive in nature.

In the Cohort 2 exploratory analysis of MYD88<sup>WT</sup> patients who received BRUKINSA (N=26), CR+VGPR+PR was 50% and VGPR/CR was 27%.<sup>1,4</sup>

## Safety in WM Consistent With Established Profile

Dose reductions due to adverse reactions<sup>1</sup>  
(N=199)

Cohort 1  
**11%**  
of patients

Discontinuation rate due to adverse reactions<sup>1</sup>  
(N=199)

Cohort 1  
**2%**  
of patients

Serious adverse reactions, including fatal events, have occurred with BRUKINSA, including hemorrhage, infections, cytopenias, second primary malignancies, and cardiac arrhythmias. The most common adverse reactions (≥20%) are neutrophil count decreased, upper respiratory tract infection, platelet count decreased, rash, hemorrhage, musculoskeletal pain, hemoglobin decreased, bruising, diarrhea, pneumonia, and cough.<sup>1</sup>

<sup>1</sup>IWWM-6 criteria (Owen et al, 2015) requires complete resolution of extramedullary disease (EMD) if present at baseline for VGPR to be assessed. Modified IWWM-6 criteria (Trean, 2015) requires a reduction in EMD if present at baseline for VGPR to be assessed.<sup>5,6</sup>

<sup>2</sup>There were no CRs in either treatment arm.

<sup>3</sup>All patients in Cohort 1 were MYD88<sup>WT</sup>.

BTK=Bruton's tyrosine kinase; CI=confidence interval; CR=complete response; IRC=independent review committee; IWWM-6=6th International Workshop on Waldenström's Macroglobulinemia; MUT=mutated; ORR=overall response rate; PR=partial response; VGPR=very good partial response; WHIM=WHIM syndrome-like somatic mutation; WT=wild type.

Please see Important Safety Information on the next page and accompanying full Prescribing Information.

## Flexible Dosing Meets Patient Needs

### Two dosing options<sup>1</sup>

BRUKINSA can be taken as 160 mg twice daily or 320 mg once daily.

### No dose exchange required for dose modification<sup>1</sup>

Dose modification for ≥Grade 3 adverse reactions only requires reduction in number of capsules taken daily.



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# IMPORTANT SAFETY INFORMATION

## WARNINGS AND PRECAUTIONS

### Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax have been reported in 3.0% 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 28% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was 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 (28%), thrombocytopenia (11%), and anemia (7%) 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 4% 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 13% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 7% of patients. Other second primary malignancies included malignant solid tumors (4%), melanoma (1.4%), 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 have occurred in 2.8% 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 0.8% 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  $\geq 20\%$  of patients who received BRUKINSA (N=779) were decreased neutrophil count (56%), upper respiratory tract infection (49%), decreased platelet count (44%), rash (35%), hemorrhage (35%), musculoskeletal pain (30%), decreased hemoglobin (28%), bruising (25%), diarrhea (23%), pneumonia (22%), and cough (21%).

## DRUG INTERACTIONS

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

**CYP3A Inducers:** Avoid co-administration 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.

## INDICATION

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

Please see full [Prescribing Information including Patient Information](#).

**References:** 1. BRUKINSA. Package insert. BeiGene, Ltd; 2021. 2. Tam C, Trotman J, Opat S, et al. Phase I study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood*. 2019;134(11):851-859. 3. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood*. 2020;136(18):2038-2050. 4. Dimopoulos M, Sanz RG, Lee HP, et al. Zanubrutinib for the treatment of MYD88 wild-type Waldenström macroglobulinemia: a substudy of the phase 3 ASPEN trial. *Blood Adv*. 2020;4(23):6009-6018. 5. Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenström macroglobulinemia: update from the 11th International Workshop. *Br J Haematol*. 2013;160(2):171-176. 6. Treon SP. How I treat Waldenström macroglobulinemia. *Blood*. 2009;114(12):2375-2385.