

FOR THE TREATMENT OF ADULT PATIENTS
WITH MANTLE CELL LYMPHOMA (MCL)¹



100%, 24-hour inhibition of BTK was maintained in peripheral blood when taken as 160 mg twice a day or 320 mg once a day.

THE BTK INHIBITOR DEMONSTRATED TO PROVIDE COMPLETE AND SUSTAINED INHIBITION^{1,2}

INDICATION

BRUKINSA™ (zanubrutinib) is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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 bleeding events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Please see additional Important Safety Information throughout, and full Prescribing Information.

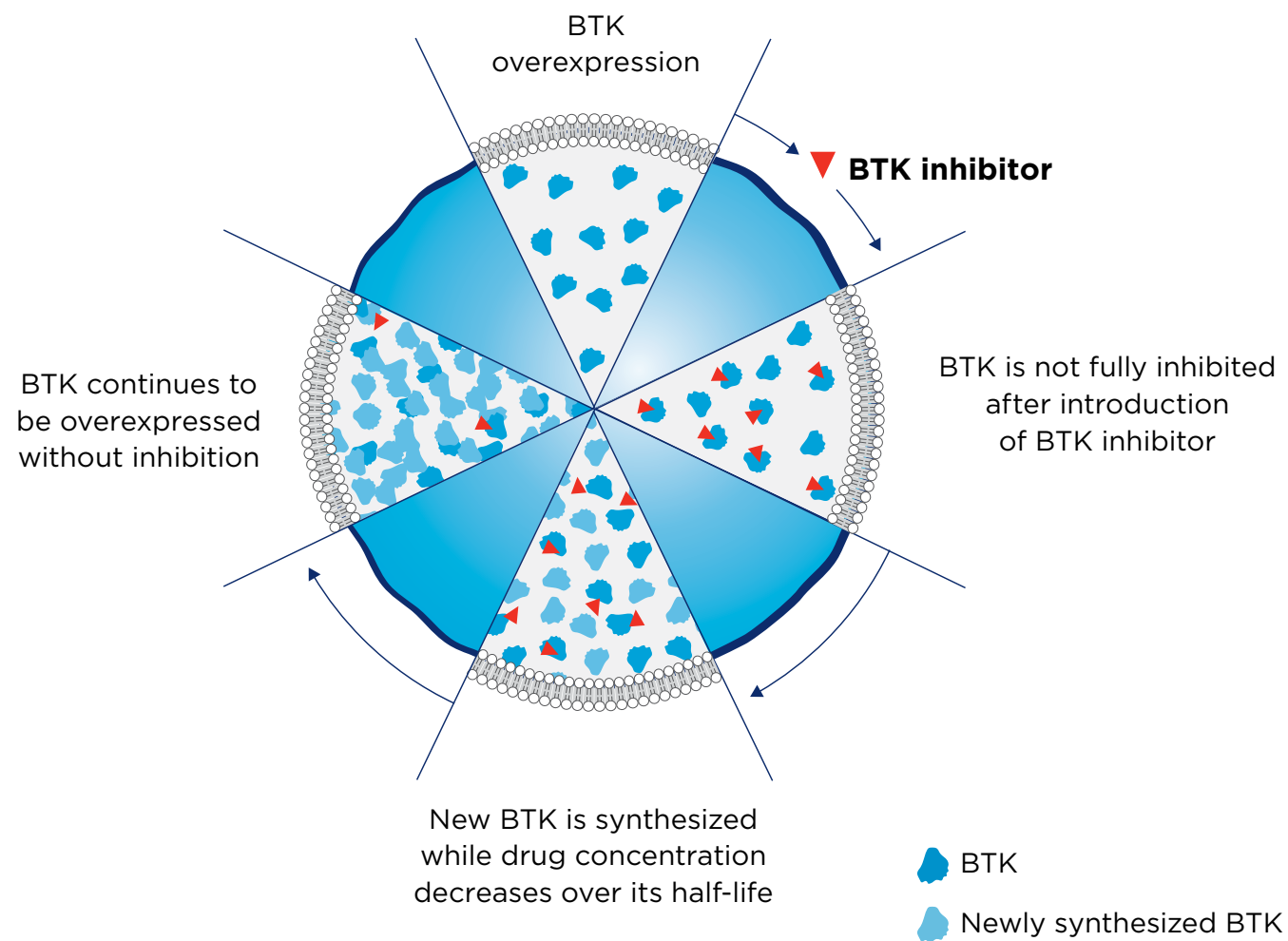


BRUTON'S TYROSINE KINASE (BTK) PROMOTES THE GROWTH AND SURVIVAL OF MALIGNANT B CELLS³

Sustained inhibition of BTK must be maintained at therapeutic concentrations in target tissues⁴

There are **key challenges** to inhibiting BTK

Challenge BTK requires 100% inhibition that is maintained around the clock because it is continuously synthesized^{4,5}



Challenge BTK inhibitor concentrations need to be sustained across disease-relevant tissues to prevent areas of unchecked disease^{4,6}

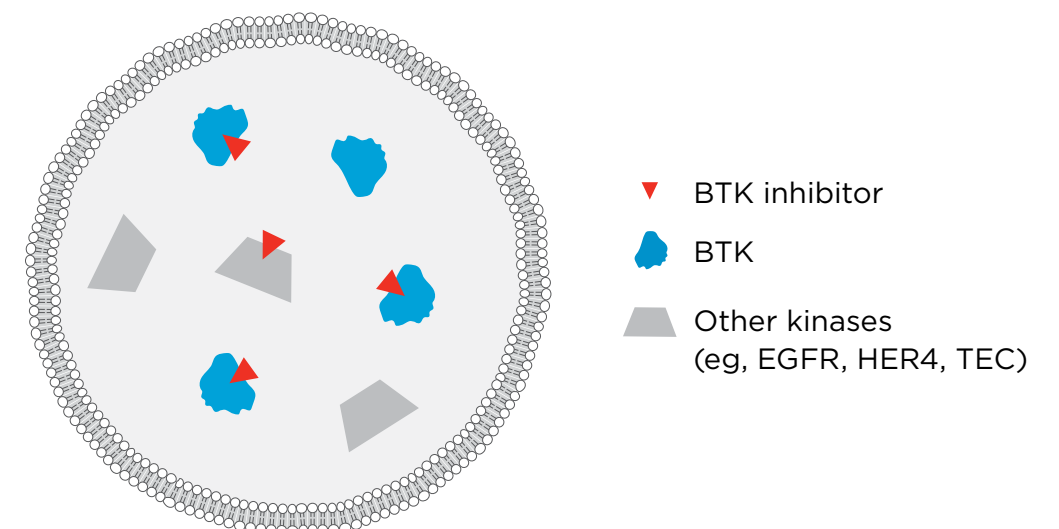


Lymph nodes



Peripheral blood mononuclear cells (PBMCs)

Challenge BTK must be selectively targeted to potentially limit adverse effects⁷



BRUKINSA WAS DESIGNED TO COMPLETELY SHUT OFF BTK

Designed to optimize bioavailability, half-life, and selectivity to meet the challenges of BTK inhibition

1 Potent and sustained inhibition

100%, 24-hour inhibition of BTK in PBMCs*^{1,2}

2 Target tissue exposure at therapeutic concentrations

Reaches and occupies BTK in plasma and lymph nodes^{1,2}

3 High affinity for BTK

Minimal off-target binding to other tyrosine kinases including EGFR, FGR, FRK, HER2, HER4, ITK, JAK3, LCK, and TEC⁸

*The clinical significance of 100% occupancy has not been established.

BTK=Bruton's tyrosine kinase; PBMCs=peripheral blood mononuclear cells.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Hemorrhage (continued)

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 23% 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.

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EVALUATED GLOBALLY IN 2 TRIALS IN A RANGE OF PATIENTS

Study design ^{1,9-11}	Study 206 (N=86)	Study 003 (N=32)
Description*	Phase 2, open-label, multicenter, single-arm trial	Phase 1/2, open-label, multicenter, single-arm trial
Setting	Previously treated MCL following at least 1 prior therapy	
Primary endpoint	ORR was assessed by an IRC according to the 2014 Lugano classification for non-Hodgkin lymphoma [†]	

Baseline patient characteristics ^{1,11}	Study 206 (N=86)	Study 003 (N=32)
Median age	60.5 years (range: 34-75)	70 years (range: 42-86)
Caucasian	0%	78%
Median time since diagnosis	2.5 years	4.5 years
Median prior anticancer regimens	2 (range: 1-4)	1 (range: 1-4)
Disease history		
Refractory MCL	52%	25%
Extranodal disease	71%	78%
Blastoid variant of MCL	14%	6%
Prior ASCT	4%	16%
Most common prior regimens		
CHOP-based	91%	59%
Rituximab-based	74%	94%
MIPI score		
Low risk	58%	28%
Intermediate risk	29%	41%
High risk	13%	31%

*In Study BGB-3111-206 (Study **206**), patients were enrolled in China. In Study BGB-3111-AU-003 (Study **003**), patients were enrolled in Australia, New Zealand, Europe, Asia, and the US.

[†]In Study **206**, PET scans were required for response assessment. In Study **003**, PET scans were not required for response assessment and the majority of patients were assessed by CT scan.

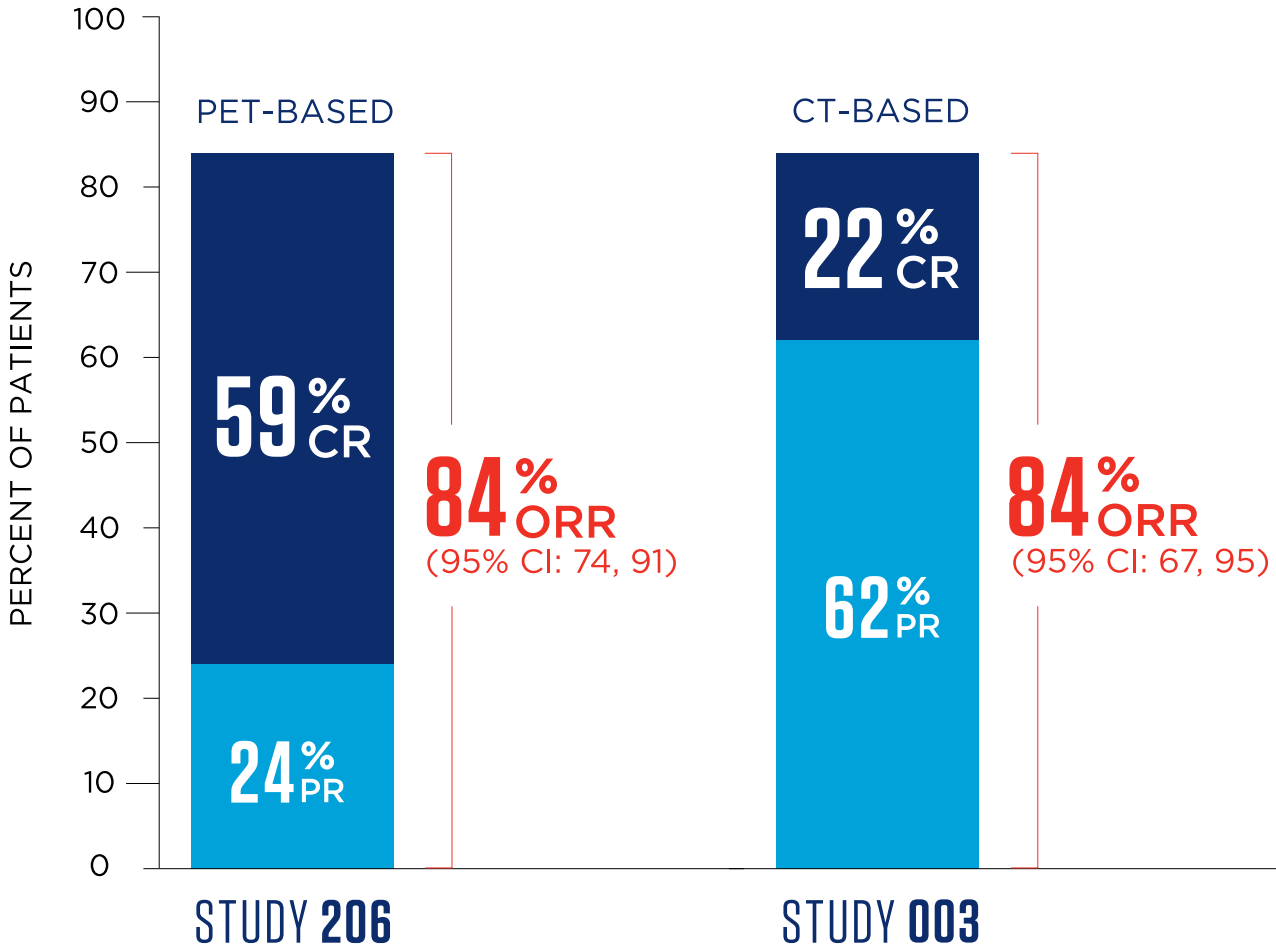
ASCT=autologous stem cell transplant; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; CT=computed tomography; IRC=independent review committee; MCL=mantle cell lymphoma; MIPI=mantle cell lymphoma international prognostic index; ORR=overall response rate; PET=positron emission tomography.

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POWERFUL RESPONSES

84% of patients responded to BRUKINSA across both studies¹



Median follow-up time was 18.4 months for Study 206 and 18.8 months for Study 003¹¹

The efficacy of BRUKINSA was IRC-assessed in 2 clinical trials that included a total of 118 adult patients with MCL who received at least 1 prior therapy. Study 206: N=86, Phase 2, open-label, multicenter, single-arm trial; PET scans were required for response assessment. Study 003: N=32, Phase 1/2, open-label, global, multicenter, single-arm trial; PET scans were not required for response assessment and the majority of patients were assessed by CT scan.

CI=confidence interval; CR=complete response; CT=computed tomography; IRC=independent review committee; ORR=overall response rate; PET=positron emission tomography; PR=partial response.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Infections (continued)

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

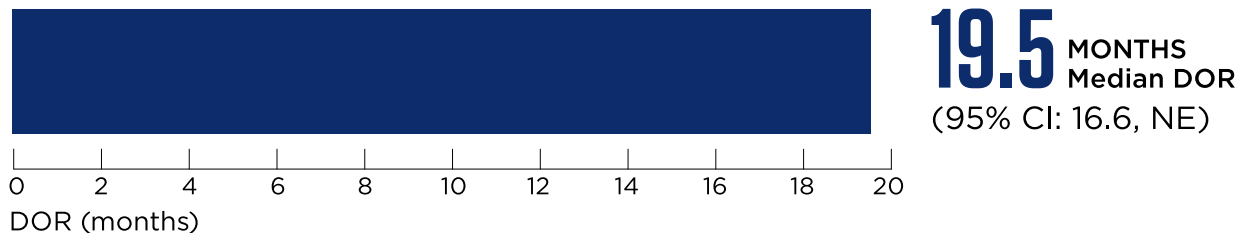
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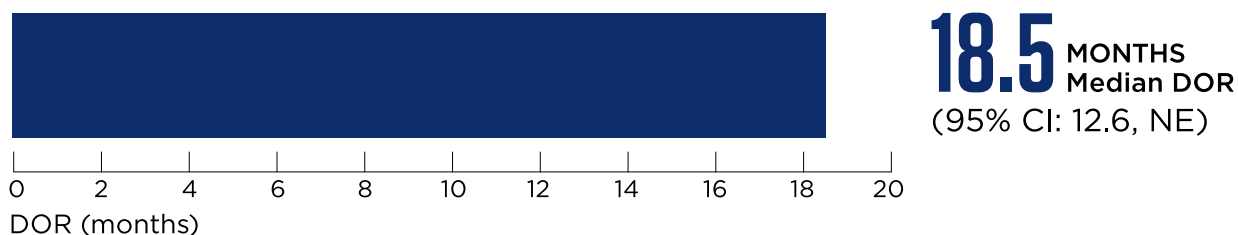
SUSTAINED RESULTS

Most patients responded for more than 18 months¹

STUDY 206



STUDY 003



Median follow-up time was 18.4 months for Study 206 and 18.8 months for Study 003¹¹

DOR=duration of response; NE=not estimable.

WARNINGS AND PRECAUTIONS (continued)

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

Cardiac Arrhythmias

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Please see additional Important Safety Information throughout, and full Prescribing Information.



DEMONSTRATED SAFETY PROFILE

Combined adverse reactions (ARs) in $\geq 10\%$ of patients with MCL (N=118)¹

Adverse reactions	All Grades (%)	Grade ≥ 3 (%)
Upper respiratory tract infection	39	0
Neutropenia and Neutrophil count decreased	38	15
Rash	36	0
Thrombocytopenia and Platelet count decreased	27	5
Leukopenia and White blood count decreased	25	5
Diarrhea	23	0.8
Pneumonia	15	10
Anemia and Hemoglobin decreased	14	8
Musculoskeletal pain	14	3.4
Hypokalemia	14	1.7
Bruising	14	0
Constipation	13	0
Hypertension	12	3.4
Cough	12	0
Hemorrhage	11	3.4
Urinary tract infection	11	0.8

The most common ARs ($\geq 20\%$; pooled safety population N=629) included neutrophil count decreased (53%), platelet count decreased (39%), upper respiratory tract infection (38%), white blood cell count decreased (30%), hemoglobin decreased (29%), rash (25%), bruising (23%), diarrhea (20%), and cough (20%).

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DEMONSTRATED SAFETY PROFILE (continued)

Combined incidence of cardiac arrhythmias in patients with hematologic malignancies (N=629)¹

Adverse reaction	All Grades (%)	Grade \geq 3 (%)
Atrial fibrillation and atrial flutter	2.0	0.6

COMBINED DOSE REDUCTION AND DISCONTINUATION RATES¹

Median duration of treatment: 17.5 months (range: 0.2-33.9 months)¹¹

Dose reductions
due to ARs

0.8%

(1/118)
of patients

Discontinuation rate
due to ARs

7%

(8/118)
of patients

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

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 at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 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.

SPECIFIC POPULATIONS

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

Please see additional Important Safety Information throughout, and full Prescribing Information.



BRUKINSA DOSING FLEXIBILITY

- BRUKINSA can be taken as 160 mg twice a day or 320 mg once a day¹
- BRUKINSA can be co-administered with proton pump inhibitors and H2-receptor antagonists¹
- BRUKINSA can be taken with or without food (advise patients to swallow capsules whole—do not open, break, or chew)¹
- BRUKINSA was allowed to be co-administered with anticoagulation therapies in clinical trials (as long as INR was ≤ 1.5 and aPTT $\leq 1.5 \times \text{ULN}$)^{10,11}

BRUKINSA should be taken until disease progression or unacceptable toxicity¹

Recommended dose modification for \geq Grade 3 adverse reactions¹

Event

- Grade 3 or higher non-hematological toxicities
- Grade 3 febrile neutropenia
- Grade 3 thrombocytopenia with significant bleeding
- Grade 4 neutropenia (lasting more than 10 consecutive days)
- Grade 4 thrombocytopenia (lasting more than 10 consecutive days)

Dose Modification

(Starting Dose: 160 mg twice daily or 320 mg once daily)

1ST OCCURRENCE	2ND OCCURRENCE	3RD OCCURRENCE	4TH OCCURRENCE
Interrupt BRUKINSA Once toxicity has resolved to recovery to Grade 1 or lower or baseline: resume at 160 mg twice daily or 320 mg once daily	Interrupt BRUKINSA Once toxicity has resolved to recovery to Grade 1 or lower or baseline: resume at 80 mg twice daily or 160 mg once daily	Interrupt BRUKINSA Once toxicity has resolved to recovery to Grade 1 or lower or baseline: resume at 80 mg once daily	Discontinue BRUKINSA

aPTT=activated partial thromboplastin time; INR=International Normalized Ratio; ULN=upper limit of normal.

IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS

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

CYP3A Inducers: Avoid coadministration with moderate or strong CYP3A inducers.

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Dedicated Oncology Nurse Advocates provide personalized support for each patient's needs



Simplifying access

- Assists with insurance verification and prior authorization support
- Co-pay as little as \$0/prescription for commercially insured patients*
- Bridge supply for insurance coverage delays[†]
- Free product for uninsured and underinsured patients[‡]



Educating patients

- Helps provide information about their disease and treatment with BRUKINSA
- Patient and caregiver follow-up support
- Dedicated Oncology Nurse Advocates for practices, patients, and caregivers



Securing support

- Assists patients and caregivers with practical help through connecting patients with advocacy groups and local/national free resources such as:
 - Counseling services
 - Support group information
 - Transportation/lodging assistance

*No patient income requirement. Annual benefit limit of \$25,000. Patients are ineligible if prescriptions are payable by any state or other federally funded programs, including, but not limited to, Medicare, Medicaid, VA, or TRICARE, or where prohibited by law. Eligibility criteria and restrictions apply.

[†]15-day supply of medication (for on-label use only) in case of a coverage delay lasting longer than 5 days. Eligibility criteria and restrictions apply.

[‡]Certain financial and eligibility criteria apply.

References: **1.** BRUKINSA [package insert]. BeiGene, Ltd; 2019. **2.** Tam C, Trotman J, Opat S, et al. Phase 1 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.** Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. *Mol Cancer*. 2018;17(1):57. **4.** Daryae F, Zhang Z, Gogarty KR, et al. A quantitative mechanistic PK/PD model directly connects Btk target engagement and in vivo efficacy. *Chem Sci*. 2017;8(5):3434-3443. **5.** Woyach JA, Johnson AJ, Byrd JC. The B-cell receptor signaling pathway as a therapeutic target in CLL. *Blood*. 2012;120(6):1175-1184. **6.** LeBien TW, Tedder TF. B lymphocytes: how they develop and function. *Blood*. 2008;112(5):1570-1580. **7.** Stephens DM, Spurgeon SE. Ibrutinib in mantle cell lymphoma patients: glass half full? Evidence and opinion. *Ther Adv Hematol*. 2015;6(5):242-252. **8.** Guo Y, Liu Y, Hu N, et al. Discovery of zanubrutinib (BGB-3111), a novel, potent, and selective covalent inhibitor of Bruton's tyrosine kinase. *J Med Chem*. 2019;62(17):7923-7940. **9.** BeiGene. Study of evaluate efficacy and safety of BGB-3111 in subjects with relapsed or refractory mantle cell lymphoma (MCL). ClinicalTrials.gov website. NCT03206970. <https://clinicaltrials.gov/ct2/show/NCT03206970>. Last updated August 20, 2019. Accessed September 12, 2019. **10.** BeiGene. Study of the safety and pharmacokinetics of BGB-3111 in subjects with B-cell lymphoid malignancies. ClinicalTrials.gov website. NCT02343120. <https://clinicaltrials.gov/ct2/show/NCT02343120>. Last updated May 31, 2019. Accessed September 12, 2019. **11.** Data on file. BeiGene, Ltd. 2019. **12.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas V.1.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed February 10, 2020. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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STUDY 206 | PET-BASED¹

84%_{ORR} **59%**_{CR} **19.5**_{mo}
(95% CI: 74, 91) **MEDIAN DOR**
(95% CI: 16.6, NE)

STUDY 003 | CT-BASED¹

84%_{ORR} **22%**_{CR} **18.5**_{mo}
(95% CI: 67, 95) **MEDIAN DOR**
(95% CI: 12.6, NE)

Median follow-up time was 18.4 months for Study 206 and 18.8 months for Study 003¹¹

Zanubrutinib (BRUKINSA[™]) is included as a second-line therapy option for MCL in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®])¹²



Zanubrutinib is a preferred regimen for short response duration (< expected median PFS) and extended response duration (> expected median PFS) to prior chemoimmunotherapy

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BTK=Bruton's tyrosine kinase; CI=confidence interval; CR=complete response; CT=computed tomography; IRC=independent review committee; NCCN=National Comprehensive Cancer Network; NE=not estimable; ORR=overall response rate; PET=positron emission tomography; PFS=progression-free survival.

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