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NCCN Guidelines Panel: B-Cell Lymphomas

On behalf of BeiGene, Ltd., I respectfully request the NCCN (B-Cell Lymphomas Guidelines Panel) to review the enclosed materials for the inclusion of BRUKINSA™ (zanubrutinib) for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

I would also like to acknowledge the contributions of the NCCN panel members who are investigators on zanubrutinib clinical studies and co-authors or co-contributors to some of these publications.

Specific Change: Please consider the inclusion of zanubrutinib as a treatment option under preferred regimens for the second-line therapy of MCL (MANT-A, NHODG-E).

FDA Clearance: Zanubrutinib was granted [breakthrough therapy designation](#) by the FDA on January 11, 2019. On November 14, 2019, zanubrutinib was approved by the FDA under the brand name BRUKINSA™ for the treatment of adult patients with 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.¹

Rationale: Zanubrutinib is a potent, selective, and irreversible oral BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases^{2,3}. The FDA approval was based on two clinical trials: BGB-3111-206 (NCT03206970) and BGB-3111-AU-003 (NCT02343120), which included a total of 118 patients with MCL who have received at least one prior therapy.^{1,4,5}

Summary of clinical efficacy data from the phase 2 study:¹

- The single-arm, open-label, multicenter, phase 2 study (BGB-3111-206, NCT03206970) evaluated a total of 86 patients with relapsed/refractory MCL. These patients received zanubrutinib 160 mg orally twice daily.
- The primary endpoint was overall response rate (ORR) as assessed by an independent review committee (IRC) using PET-based imaging according to the Lugano Classification 2014.
- The median age was 60.5 years (range, 34-75). These patients had received 1-4 prior lines of therapy. Most were men (78%); 71% of patients had extranodal involvement, and 52% had refractory disease. 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% of patients.
- The ORR, complete response rate (CR) and partial response rate (PR) per IRC assessment were 84%, 59%, and 24%, respectively.
- The median duration of response (DoR) was 19.5 months (95% CI, 16.6-not estimable).

Summary of clinical efficacy data from the global phase 1/2 study:¹

- The multicenter, open-label, phase 1/2 study of B-cell malignancies (BGB-3111-AU-003, NCT02343120) included 32 patients with relapsed/refractory MCL. These patients received zanubrutinib 160 mg orally twice daily or 320 mg orally daily.
- Efficacy was assessed using CT imaging in most patients (PET imaging was optional per protocol).^{1,5}
- The median age was 70 years (range, 42-86), and 38% of patients were ≥75 years old. Most patients were men (69%). The MIPI score was low in 28%, intermediate in 41% and high risk in 31% of patients.
- The ORR, CR and PR per IRC assessment were 84%, 22%, and 62%, respectively.
- The median DoR was 18.5 months (95% CI; 12.6-not estimable).

Summary of combined safety data in patients with relapsed/refractory MCL treated with zanubrutinib:¹

- In the 118 patients with MCL who received at least 1 prior line of therapy treated with zanubrutinib in the BGB-3111-206 and BGB-3111-AU-003 studies, 79% and 68% of patients received zanubrutinib for ≥ 6 months and >12 months, respectively.
- The most common adverse reactions ($\geq 20\%$) of any grade were upper respiratory tract infection (39%), neutropenia (38%), rash (36%), thrombocytopenia (27%), leukopenia (25%), and diarrhea (23%).
- Serious adverse reactions were reported in 31% of patients; pneumonia (11%) and hemorrhage (5%) were the most frequent reactions.
- Treatment discontinuation due to adverse reactions occurred in 7% of patients, with pneumonia (3.4%) as the most common. Dose reduction due to an adverse reaction (hepatitis B) occurred in 1 patient (0.8%).

Summary of cumulative safety experience with zanubrutinib:¹

- A pooled safety analysis was reported for 629 patients with B-cell malignancies treated in 5 zanubrutinib monotherapy studies (including MCL, Waldenström macroglobulinemia, chronic lymphocytic leukemia/small lymphocytic lymphoma, diffuse large B-cell lymphoma, and others); 524 patients received zanubrutinib 160 mg orally twice daily, and 105 patients received zanubrutinib 320 mg orally daily.^{1,6}
- Among these patients, zanubrutinib exposure was ≥ 6 months in 79% and >12 months in 61% of patients.
- The most common adverse reactions in $\geq 10\%$ of patients were 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%), cough (20%), musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

Please refer to the BRUKINSA™ package insert for the FDA-approved indication, dosage and administration, and safety information.¹ In addition, the following articles are submitted in support of the proposed change and to provide additional context on the properties of zanubrutinib.²⁻⁹ Should you have any questions, please do not hesitate to contact me.

References

1. BRUKINSA™ (zanubrutinib) capsules [package insert]. BeiGene, Ltd; San Mateo, CA. November 2019.
2. Tam CSL, Trotman J, Opat S, Burger JA, Cull G, Gottlieb DJ, et al. Phase 1 study of selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL [supplemental appendix appears online]. *Blood*. 2019;134(11):851-859. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31340982>.
3. Guo Y, Liu Y, Hu N, Yu D, Zhou C, Shi G, 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31381333>.
4. Song Y, Zhou K, Zou D, Hu JZJ, Yang H, Zhang H, et al. Zanubrutinib in patients with relapsed/refractory mantle cell lymphoma. *Hematol Oncol*. 2019;37(S2):45-46.
5. Tam C, Wang M, Simpson D, Opat S, Cull G, Munoz J, et al. Updated safety and efficacy data in the phase 1/2 trial of zanubrutinib in patients with mantle cell lymphoma. Presented at: International Conference on Malignant Lymphoma; June 18-22, 2019; Lugano, Switzerland.
6. Tam C, Opat S, Zhu J, Cull G, Gottlieb D, Li J, et al. Pooled analysis of safety data from monotherapy studies of the Bruton tyrosine kinase (BTK) inhibitor, zanubrutinib (BGB 3111) in B cell malignancies. Presented at: European Hematology Association Congress; June 13-16, 2019; Amsterdam, The Netherlands.
7. Song Y, Qi J, Xu W, Li D, Zhou J, Li J, et al. A phase I clinical study to investigate the safety, tolerability and pharmacokinetics/pharmacodynamics of BTK inhibitor BGB-3111 in Chinese patients with B-cell lymphoma. Presented at: Annual Meeting of the Chinese Society of Clinical Oncology; September 19-23, 2018; Xiamen, China.
8. Tam C, Simpson D, Opat S, Kim W, Wang M, Cull G, et al. Safety and activity of the highly specific BTK inhibitor zanubrutinib (BGB-3111) in patients with indolent and aggressive non-Hodgkin's lymphoma. Presented at: American Society of Hematology Annual Meeting; December 9-12, 2017; Atlanta, Georgia.
9. Dobie G, Sze D, Tam C, Jackson D. The effect of BTK inhibitors on haemostasis and thrombosis. Presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, California.