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Date of request: July 31, 2020
NCCN Guidelines Panel: Multiple Myeloma/Systemic Light Chain Amyloidosis/Waldenström's Macroglobulinemia Panel

BeiGene, Ltd. respectfully requests that the NCCN (Multiple Myeloma/Systemic Light Chain Amyloidosis/Waldenström's Macroglobulinemia Guidelines Panel) reviews the enclosed materials in support of the inclusion of zanubrutinib for the treatment of patients with Waldenström macroglobulinemia (WM).

I would 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 preferred option in patients requiring primary therapy for WM (WM/LPL-B, 1 OF 3) and in patients who were previously treated for WM (WM/LPL-B, 2 OF 3).

FDA Clearance: Zanubrutinib (BRUKINSA®) was approved by the FDA for the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy.[1] 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. Zanubrutinib was granted fast track designation by the FDA for the treatment of patients with WM in July 2018.

Rationale: The safety and efficacy of zanubrutinib for the treatment of WM were demonstrated in two clinical trials.[2-5] The phase 3 ASPEN trial is the largest prospective study conducted to date in WM and the first phase 3 study comparing two BTK inhibitors head-to-head in any indication.[2,3] While not statistically significant by independent review, for $MYD88^{mut}$ patients, a higher CR/VGPR rate was observed for zanubrutinib vs ibrutinib. The incidence and severity of most BTK-associated toxicities (including atrial fibrillation, hemorrhage, pneumonia, and diarrhea) as well as adverse events leading to dose reductions and treatment discontinuation were lower with zanubrutinib than ibrutinib (results below).

In the exploratory non-randomized cohort of ASPEN, the largest cohort of confirmed $MYD88^{WT}$ WM patients studied with a BTK inhibitor, 50% of patients achieved a major response, and 26.9% achieved a VGPR.[4] In the phase 1/2 BGB-3111-AU-003 study, 77 patients with WM were treated with zanubrutinib and followed for 3 years.[5] Long-term treatment of zanubrutinib resulted in an ORR of 96% and CR/VGPR rate of 45%. Among patients with $MYD88^{WT}$ WM, an ORR of 100%, CR/VGPR rate of 25%, and a MRR of 62.5% were achieved. Treatment was generally well tolerated in both treatment naïve and relapsed/refractory WM patients.

Phase 3 Head-to-Head Study of Zanubrutinib vs Ibrutinib in Patients with WM:[2-4]

- The phase 3 ASPEN trial (BGB-3111-302, NCT03053440) included a randomized cohort of 201 patients with WM harboring a MYD88 mutation and a non-randomized cohort of 26 patients with $MYD88^{WT}$ WM.
- The randomized cohort of the trial compared zanubrutinib 160 mg twice daily with ibrutinib 420 mg once daily in patients with MYD88 mutation-positive WM.[2] Overall, 164 patients had relapsed/refractory disease and 37 were treatment naïve. Results were reported as of a median follow-up of 19.4 months.

- For the primary endpoint of VGPR or better assessed by independent review, VGPR rates with zanubrutinib vs ibrutinib were 28% vs 19% (p=0.09). No CRs were observed.
    - Investigator-assessed rates of VGPR were 28% and 17% in the zanubrutinib and ibrutinib arms, respectively (nominal p=0.04).
- The median times to achieve a VGPR were 5.6 months with zanubrutinib and 22.1 months with ibrutinib in treatment naïve patients and were comparable among relapsed/refractory patients at 4.7 months and 5.1 months, respectively.
- The 18-month PFS rates for zanubrutinib vs ibrutinib were 85% vs 84%, and the 18-month OS rates were 97% vs 93%, respectively.
- IgM reductions from baseline over time were significantly greater and more sustained with zanubrutinib vs ibrutinib.
- Zanubrutinib trended toward greater improvement in most QoL assessments, most notably in the EQ-5D and QLQ-C30 subscales of appetite, dyspnea, fatigue, physical function, and role functioning and particularly among patients who achieved a VGPR. The functional scale for diarrhea trended toward worse for ibrutinib than zanubrutinib treated patients.
- Adverse events with zanubrutinib and ibrutinib, respectively, were Grade ≥3 in 58% and 63% of patients, led to dose reductions in 14% and 23% of patients, led to treatment discontinuation in 4% and 9% of patients, and led to death in 1 patient and 2 patients. For a comprehensive list of treatment-emergent adverse events, please refer to the publication (Table 3).[2] Rates of BTK inhibitor adverse events of interest are shown in the following table.[3] Certain adverse events of interest, such as hypertension and atrial fibrillation, increased over time in the ibrutinib arm to a greater extent than the zanubrutinib arm; please refer to Slide 16 of the enclosed presentation.

Head-to-Head Comparative Safety Results for Adverse Events of Interest with BTK inhibitors[3]

Adverse Event Category (Pooled Terms), n (%)	All Grades		Grade ≥3	
	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)
Infection	67 (66.3)	66 (67.3)	18 (17.8)	19 (19.4)
Hemorrhage	49 (48.5)	58 (59.2)	6 (5.9)	8 (8.2)
Major hemorrhage*	6 (5.9)	9 (9.2)	6 (5.9)	8 (8.2)
Neutropenia†	30 (29.7)	13 (13.3)	20 (19.8)	8 (8.2)
Diarrhea	21 (20.8)	31 (31.6)	3 (3)	1 (1)
Second malignancy	12 (11.9)	11 (11.2)	2 (2)	1 (1)
Hypertension	11 (10.9)	17 (17.3)	6 (5.9)	12 (12.2)
Atrial fibrillation/flutter†	2 (2)	15 (15.3)	0	4 (4.1)

* Grade ≥3 bleeding or central nervous system bleeding of any grade.
† Descriptive 2-sided p<0.05.

- The exploratory nonrandomized cohort of ASPEN evaluated zanubrutinib 160 mg twice daily in patients with MYD88^{WT} WM.[4] Of 28 patients enrolled, 23 had relapsed/refractory disease, and 5 were treatment naïve. MYD88^{WT} WM was confirmed by a central laboratory and efficacy was evaluable in 26 patients with a median follow-up of 17.9 months. A VGPR of 26.9% and a MRR of 50% were observed. The 12-month PFS rate was 72.4%, and the 12-month OS rate was 96.2%.

Phase 1/2 Study in Patients with B-Cell Malignancies, including WM: 3 Years of Follow-up:[5]

- The Phase 1/2 BGB-3111-AU-003 trial (NCT NCT02343120) included 77 WM patients with no prior BTK inhibitor treatment; 53 patients had relapsed/refractory disease, and 24 were treatment naïve. Patients received zanubrutinib 160 mg twice daily (n=50) or 320 mg once daily (n=23).
- In 73 efficacy-evaluable patients, the ORR was 95.9%, the CR/VGPR rate was 45.2% (rate increased over time), and the MRR was 82.2%. The estimated 3-year PFS rate was 80.5%, and OS rate was 84.8%.
- Among 8 efficacy-evaluable patients with MYD88^{WT} WM, 8 (100%) achieved a response, 2 (25%) had a deep response (including 1 CR, 1 VGPR), and 5 (62.5%) had a major response.
- At three years of follow up, treatment was generally well tolerated. Atrial fibrillation/flutter, major hemorrhage, and grade ≥3 diarrhea were reported in 5.2%, 3.9%, and 2.6% patients, respectively.

The following are submitted in support of the proposed change. Should you have any questions, please do not hesitate to contact me.

References:

1. Brukinsa (zanubrutinib) [package insert]. BeiGene USA, Inc; San Mateo, CA. November 2019.
2. Tam C, et al. A randomized phase 3 trial of zanubrutinib versus ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood; 2020.
3. Tam C, et al. ASPEN: Results of a Phase 3 randomized trial of zanubrutinib versus ibrutinib for patients with Waldenström macroglobulinemia (WM). Presented at: American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual.
4. Dimopoulos M, et al. Updated results of the ASPEN trial from a cohort of patients with MYD88 wild-type Waldenstrom macroglobulinemia. Presented at: European Hematology Association; June 11-21, 2020; Virtual.
5. Trotman J, et al. Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: three years of follow-up. Blood; 2020.