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NCCN Guidelines Panel: CLL/SLL Guidelines Panel

BeiGene, Ltd. respectfully requests the NCCN (CLL/SLL Guidelines Panel) to review the enclosed materials for the inclusion of zanubrutinib for the treatment of patients with previously untreated CLL/SLL with deletion of 17p (del[17p]).

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 first-line treatment option for patients with CLL/SLL with del(17p) (CSLL-D, 3 OF 6).

FDA Clearance: Zanubrutinib (BRUKINSA®) is 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 is not currently approved by the FDA for the treatment of CLL/SLL.

Rationale: In a large, nonrandomized cohort of 109 treatment-naive patients with del(17p) CLL/SLL in the global, phase 3 SEQUOIA study, zanubrutinib monotherapy demonstrated high and durable responses (ORR 94.5%; median duration of response not reached; 93% of patients had a response duration of ≥12 months) at a median follow-up of 18.2 months.[2] The safety and tolerability of zanubrutinib have been demonstrated not only in this study with respect to CLL/SLL, but also in the phase 3 ASPEN study, the largest prospective study conducted to date in Waldenström macroglobulinemia (WM) and the first phase 3 study comparing 2 BTK inhibitors head-to-head in any indication. 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 at a median follow-up of 19.4 months.[3,4] The 3-year long-term follow-up of patients with WM in the phase 1/2 BGB-3111-AU-003 study further validates the consistent safety profile of zanubrutinib.[5]

Phase 3 Study in Patients with Previously Untreated CLL/SLL and Del(17p)[2]

- The global, phase 3, open-label SEQUOIA study (BGB-3111-304, NCT03336333) included a nonrandomized cohort of 109 treatment-naïve patients with CLL/SLL and centrally confirmed del(17p) who were treated with zanubrutinib 160 mg twice daily.
- Patients were a median of 70 years old (range, 42-86), the majority had CLL (90.8%), 38.5% had bulky disease, and 40.4% had Binet stage C disease. Many patients had other high-risk disease characteristics. Among patients with available test results, 78.8% had elevated β2-microglobulin, 65% had unmutated IGHV, and 37.2% had at least 3 distinct karyotypic abnormalities defined as complex karyotype.
- Results were reported after a median follow-up of 18.2 months.
- The ORR was 94.5%, including CR in 2.8%, CR with incomplete hematologic recovery in 0.9%, PR in 87.2%%, and PR-L in 3.7%.
- The median time to response was 2.8 months.
- Median duration of response was not reached; response duration was ≥12 months in 93% of patients.
- Median PFS and OS were not reached. The estimated 18-month PFS and OS rates were 88.6% and 95.1%, respectively.

- Adverse events of special interest for BTK inhibitors that occurred in ≥10% of patients included infections (64.2%, 13.8% grade ≥3), minor bleeding (26.6%), bruising (24.8%, 0% grade ≥3), neutropenia (18.3%, 13.8% grade ≥3), diarrhea (15.6%, 0.9% grade ≥3), nausea (13.8%, 0% grade ≥3), arthralgia (11%, 0% grade ≥3), and fatigue (10.1%, 0.9% grade ≥3)
- Grade ≥3 adverse events were reported in 48.6% of patients; neutropenia/decreased neutrophil count (12.9%) and pneumonia (3.7%) were the most common. Adverse events led to dose reduction in 6 patients (5.5%), to discontinuation in 4 patients, and to death in 2 patients (including 1 in the setting of progressive disease).

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

- The phase 3 ASPEN trial (BGB-3111-302, NCT03053440) included a cohort of 201 patients with WM harboring a MYD88 mutation who were randomized to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily.[3] Results were reported as of a median follow-up of 19.4 months.
- 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).[3] Rates of BTK inhibitor adverse events of interest are shown in the following table.[4] Although a higher rate of neutropenia was associated with zanubrutinib compared to ibrutinib, it did not translate to an increased rate of infections. 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[4]

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.

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 patients with WM who received zanubrutinib 160 mg twice daily or 320 mg once daily.
- At three years of follow-up, adverse events of interest included infections (90.9%, 27.3% grade ≥3), contusion (32.5%, all grade 1), neutropenia (18.2%), major hemorrhage (3.9%), atrial fibrillation/flutter (5.2%), and grade 3 diarrhea (2.6%).

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 CS, Robak T, Ghia P, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukemia and 17p deletion. Submitted to: Haematologica 2020.
3. Tam C, et al. A randomized phase 3 trial of zanubrutinib versus ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood; 2020.
4. 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.
5. Trotman J, et al. Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: three years of follow-up. Blood; 2020.