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NCCN Guidelines Panel: CLL/SLL Guidelines Panel

On behalf of BeiGene, Ltd., I respectfully request the NCCN (CLL/SLL Guidelines Panel) to review the enclosed materials for the inclusion of BRUKINSA™ (zanubrutinib) for the treatment of patients with CLL/SLL.

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 for first-line CLL/SLL with del(17p)/TP53 mutation and for relapsed/refractory CLL/SLL with/without del(17p)/TP53 mutation (Category 2A).

FDA Clearance: On November 14, 2019, zanubrutinib was approved by the FDA under the brand name BRUKINSA™ 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: 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]

Data from the nonrandomized cohort of the phase 3 study in patients with previously untreated CLL/SLL:[4]

- In the global, phase 3, open-label SEQUOIA study (BGB-3111-304, NCT03336333), a nonrandomized cohort of 109 treatment-naïve patients with CLL/SLL harboring del(17p) were treated with zanubrutinib 160 mg twice daily (Arm C).
- Patients had a median age of 70 years (range, 42-86); 38.5% had bulky disease.
- As of August 7, 2019, after a median follow-up of 10 months, ORR was 92.7% (CR 1.9%, PR 78.9%, PR-L 11.9%). The median time to response was 2.8 months; duration of response was ≥6 months in 95% of patients. Median PFS was not reached.

Data from the global phase 1/2 study in treatment-naïve or relapsed/refractory CLL/SLL patients:[2,5]

- BGB-3111-AU-003 (NCT02343120) was a global, multicenter, phase 1/2 study of zanubrutinib in patients with B-cell malignancies. The results for 94 patients with CLL/SLL were previously published.[2]
- A recent update was presented at ASH 2019; study enrollment was complete with a total of 123 CLL/SLL patients. Patients had a median age of 67 years (range, 24-87); 17.1% were ≥75 years old; 38.2% had bulky disease.
- As of May 8, 2019, the median follow-up was 29.5 months; the median treatment duration was 25.8 months.
- In the overall CLL/SLL population, ORR was 95.9% (CR 15.4%, CRi 0.8%, PR 73.2%, PR-L 6.5%) with response improving over time; 97.2% of responders remained in response at 12 months. Among the 16 patients with del(17p); ORR was 93.8% (CR 6.3%, PR 75%, PR-L 12.5%); 100% of responders remained in response at 12 months.
- In the 22 treatment-naïve CLL/SLL patients, ORR was 100% (CR 22.7%, PR 77.3%); 95.2% of responders remained in response at 12 months. At a median PFS follow-up of 32.2 months, the estimated PFS rates at 12 and 24 months were 95%. Among the 3 treatment-naïve patients with del(17p), ORR was 100% (all PR), and all remained in response at 12 months.
- Among the 101 patients with relapsed/refractory CLL/SLL, the median number of prior therapies was 2 (range, 1-10). Del(17p), TP53 mutation, del(11q), and unmutated IGHV were present in 16.2%, 31%, 23.5% and 68.3% of patients, respectively. ORR was 95% (CR 13.9%, CRi 1%, PR 72.3%, PR-L 7.9%); 97.6% of responders remained in response at 12 months. At a median PFS follow-up of 23.1 months, the estimated PFS rates at 12 and 24 months were 97% and 91%, respectively. In the 13 relapsed/ refractory CLL/SLL patients with del(17p), ORR was 92.3% (CR 7.7%, PR 69.2%, PR-L 15.4%); all responders remained in response at 12 months. [5]

Data from the phase 2 study conducted in China in patients with relapsed/refractory CLL/SLL:[6]

- The single-arm, open-label, multicenter, phase 2 BGB-3111-205 study (NCT03206918) included 91 patients in China with relapsed/refractory CLL/SLL. Patients received zanubrutinib 160 mg twice daily.
- Patients had a median age of 61 years (range, 35-87); 79.1% had disease refractory to last therapy, and 44.4% had bulky disease. TP53 mutation/del(17p) was present in 24.4% of patients.
- As of December 14, 2018, after a median follow-up of 15.1 months, ORR was 84.6% (CR 3.3%, PR 59.3%, PR-L 22%). Median PFS was not reached; the PFS rates at 6 and 12 months were 92.2% and 87.2%, respectively.
- ORR was 86.4% in patients with del(17p) and 82.4% in patients with unmutated IGHV.

Summary of cumulative safety experience with zanubrutinib:[7]

- In a pooled safety analysis conducted in 682 patients with B-cell malignancies treated in 6 ongoing zanubrutinib monotherapy studies (including MCL, WM, CLL/SLL, DLBCL, and others), patients had a median age of 64 years with 15% aged ≥75 years (range, 20-90), and most patients (91%) had relapsed/refractory disease.
- The median duration of zanubrutinib exposure was 13.4 months; 57% of patients had ≥12 months of exposure; 5% were treated for ≥36 months. The median relative dose intensity was 99.8% (range, 99.1-100).
- The most common adverse events reported in ≥10% of patients were upper respiratory tract infection, absolute neutrophil count (ANC) decreased, diarrhea, cough, contusion, rash, anemia, platelet count decreased, urinary tract infection, white blood cell count decreased, constipation and fatigue.
- Opportunistic infections reported in >1 patient were herpes simplex, bronchopulmonary aspergillosis, and cryptococcal meningitis.
- Adverse events of special interest including atrial fibrillation/flutter, major hemorrhage, and grade ≥3 hypertension were reported in 1.9%, 2.5%, and 3.4% of patients treated with zanubrutinib monotherapy, respectively. The exposure-adjusted incidence rates were 0.13 events/100 patient-months for atrial fibrillation/flutter of any grade, 0.17 events/100 patient-months for major hemorrhage of any grade, and 0.24 events/100 patient-months for grade ≥3 hypertension. Patients have been allowed to receive anticoagulant and antiplatelet agents.

Please refer to the BRUKINSA™ package insert for the FDA-approved indication, dosage and administration, and safety information.[1] Additional references are submitted in support of the proposed change, including the high-level information on the comparative safety data for zanubrutinib vs. ibrutinib in the global phase 3 study in WM.[8-12]

References

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