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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, updated materials for the inclusion of zanubrutinib for the treatment of patients with relapsed/refractory CLL/SLL.

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 treatment option for patients with relapsed/refractory CLL/SLL with/without del(17p)/TP53 mutation (Category 2A).

FDA Clearance: On November 14, 2019, 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 is not currently approved by the FDA for the treatment of CLL/SLL.

Rationale: The safety and efficacy of zanubrutinib for the treatment of CLL/SLL were demonstrated in three separate clinical trials.[2-5] In these trials, a total of 192 patients with relapsed/refractory CLL/SLL treated with zanubrutinib monotherapy showed durable benefits at a median follow-up ranging from 15.1 to 29.5 months.[2-4] These results have been published in *Blood 2019*[2] and this week in *Journal of Hematology & Oncology 2020*.[4] The safety and tolerability of zanubrutinib were previously reported in an aggregated 629-patient dataset.[1] As well, the phase 3, head-to-head ASPEN trial comparing zanubrutinib vs ibrutinib in patients with Waldenström macroglobulinemia (WM) further validates the consistent safety profile of zanubrutinib, and the results after a median follow-up of 19.4 months will be presented at the upcoming ASCO virtual meeting (provided here under embargo).[6*]

Phase 1/2 Study in Patients with B-Cell Malignancies, including CLL/SLL[2-3]

- 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]
- An updated analysis was reported after study enrollment was complete with a total of 123 CLL/SLL patients and a median follow-up of 29.5 months.[3]
- Patients had a median age of 67 years (range, 24-87); 38.2% had bulky disease. 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.
- In the overall CLL/SLL population, the 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), the 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, the 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), the ORR was 100% (all PR), and all remained in response at 12 months.

*Information is embargoed prior to presentation: Abstract 8007, available 5/29/20 at https://meetinglibrary.asco.org/session/12658.

- In the 101 patients with relapsed/refractory CLL/SLL, the 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), the ORR was 92.3% (CR 7.7%, PR 69.2%, PR-L 15.4%); all responders remained in response at 12 months.

Phase 2 Study in Patients with Relapsed/Refractory CLL/SLL[4]

- The single-arm, open-label, multicenter, phase 2 BGB-3111-205 study (NCT03206918) evaluated zanubrutinib 160 mg twice daily in 91 patients in China with relapsed/refractory CLL/SLL.
- Results were published recently after a median follow-up of 15.1 months.
- Patients were a median of 61 years old (range, 35-87); 79.1% had disease refractory to last therapy, 44% had bulky disease, and 24.2% had disease harboring a del(17p) or TP53 mutation.
- The ORR was 84.6% (CR 3.3%, PR 59.3%, PR-L 22%). An estimated 92.9% of responders remained in response at 12 months.
- At a median PFS follow-up of 12.9 months, median PFS was not reached, and the 12-month PFS rate was 87.2%. The estimated 12-month OS rate was 95.6%.
- The ORR was 86.4% in patients with del(17p) or TP53 mutation and 82% in patients with unmutated IGHV.

Phase 3 Study in Patients with Previously Untreated CLL/SLL and Del(17p)[5]

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

Aggregate Safety Dataset[1]

- A pooled safety analysis was reported for 629 patients with B-cell malignancies treated in 5 zanubrutinib monotherapy studies; 524 patients received zanubrutinib 160 mg twice daily, and 105 patients received zanubrutinib 320 mg daily.
- Overall, 79% of patients were treated for ≥6 months, and 61% were treated for >1 year.
- The most common adverse reactions in >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%).

Phase 3 Head-to-Head Study of Zanubrutinib vs Ibrutinib in Patients with WM[6*]

- The ASPEN trial (BGB-3111-302, NCT03053440) is the first randomized, phase 3 study comparing 2 BTK inhibitors in any indication, and it is the largest prospective, randomized, phase 3 study in WM.
- A total of 201 patients with MYD88 mutation-positive WM were randomized 1:1 to zanubrutinib vs ibrutinib.
- After a median follow-up of 19.4 months, in the zanubrutinib vs ibrutinib arm, respectively, grade ≥3 adverse events (AEs) were 58.4% vs 63.3%, AEs led to treatment discontinuation in 4% vs 9.2% of patients, and fatal AEs occurred in 1% vs 4.1% of patients.
- For AEs of special interest for BTK inhibitors, using all pooled terms, atrial fibrillation/flutter of any grade was 2% in the zanubrutinib arm and 15.3% in the ibrutinib arm; hemorrhage was 48.5% for zanubrutinib and 59.2% for ibrutinib; major hemorrhage was 5.9% for zanubrutinib and 9.2% for ibrutinib; diarrhea was 20.8% for zanubrutinib and 31.6% for ibrutinib; hypertension was 10.9% for zanubrutinib and 17.3% for ibrutinib; and infection was 66.3% for zanubrutinib and 67.3% for ibrutinib.

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- For zanubrutinib and ibrutinib, respectively, rates of all-grade neutropenia were 25% and 12%, and rates of all-grade pneumonia were 2% and 12%.

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

References

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6.* Tam CS, Opat S, D'Sa S, Jurczak W, Lee H-P, Cull G, 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. Available at: https://meetinglibrary.asco.org/.

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