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 (BRUKINSATM) was approved by the FDA for the treatment of adult patients with mantle cell lymphoma 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. 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 in patients with B-cell malignancies, including CLL/SLL. These results have been published in Blood 2019 and this week in Journal of Hematology & Oncology 2020. The safety and tolerability of zanubrutinib were previously reported in an aggregated 629-patient dataset. 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).

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

- **BGB-3111-AU-003 (NCT02343120)** was a global, multicenter, phase 1/2 study of zanubrutinib in patients with CLL/SLL. The results for 94 patients with CLL/SLL were previously published.
- 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.
- 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.
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
- 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)
- 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
- 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
- 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.

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
