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NCCN Guidelines® Panel: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

On behalf of AbbVie and Genentech, I respectfully request the NCCN Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) Guideline Panel to consider the enclosed, recently approved label for Venclexta® (venetoclax) in combination with Gazyva® (obinutuzumab) for first-line (1L) treatment of patients with CLL/SLL. Data from the pivotal CLL14 trial are expected to be presented at an upcoming 2019 ASCO medical meeting and published in a journal this year.

**Specific Changes:** Consider a recommendation of venetoclax plus obinutuzumab as a first-line, preferred regimen for CLL/SLL patients without del(17p)/*TP53* mutation and patients with del(17p)/*TP53* mutation.

**FDA Clearance**:

- **Venclexta® (venetoclax) in combination with Gazyva® (obinutuzumab)** is approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with CLL/SLL.
    - Please refer to Venclexta® (venetoclax) prescribing information for full FDA-approved indications and safety information, available at: https://www.rxabbvie.com/pdf/venclexta.pdf.
- **Gazyva® (obinutuzumab) in combination with Leukeran® (chlorambucil)** is approved by the US FDA for the treatment of patients with previously untreated CLL.
    - Please refer to Gazyva® (obinutuzumab) prescribing information for full FDA-approved indications and safety information, available at: https://www.gene.com/download/pdf/gazyva_prescribing.pdf.

**Rationale:** A Phase 3 randomized, controlled trial evaluated the efficacy and safety of venetoclax in combination with obinutuzumab (VenG) versus obinutuzumab in combination with chlorambucil (GClb) in previously untreated patients with CLL and coexisting medical conditions (total Cumulative Illness Rating Scale score >6; CrCl <70 mL/min).[1] Both treatment arms had a planned fixed treatment duration of 12 months (28-day cycles). Obinutuzumab was administered for 6 cycles, venetoclax and chlorambucil for a total of 12 cycles, each. Patients in the VenG arm initiated treatment with venetoclax on Day 22, Cycle 1 starting with a 5-week dose ramp-up. The major efficacy endpoint was independent review committee (IRC)-assessed progression free survival (PFS). Minimal residual disease (MRD; based on allele-specific

oligonucleotide polymerase chain reaction [ASO-PCR]) in peripheral blood and bone marrow 3 months after treatment completion, overall response rate (ORR), complete remission/ complete remission with incomplete marrow recovery (CR/CRi) rates, and overall survival were evaluated as secondary endpoints.

A total of 432 patients were randomized in the study, 216 patients to each study arm. Baseline characteristics were similar between study arms. The median treatment duration of venetoclax was 10.5 months (range, 0-13.5 months). The median number of cycles was 6 for obinutuzumab and 12 for chlorambucil.

PFS was significantly improved in the VenG arm versus the GClb arm (IRC-assessed PFS HR 0.33; 95% CI: 0.22 to 0.51, P<0.0001). Median duration of follow-up for PFS was 28 months (range, 0.1-36.0 months). After all patients were off treatment for at least 1 year, progressive events were more frequent with GClb (37%) than with VenG (13%).

MRD negativity (defined as <1 CLL cell/$10^4$ leukocytes) rates in the intent-to-treat population 3 months after completion of scheduled treatment in both peripheral blood and bone marrow were significantly higher in the VenG arm than in the GClb arm (76% vs. 35% [P<0.0001] and 57% vs. 17% [P<0.0001], respectively). Twelve months after completion of treatment, MRD negativity rates in the peripheral blood were 58% and 9% in patients treated with VenG and GClb, respectively. Overall response rates and CR/CRi rates were also higher in patients who received VenG versus GClb (85% vs 71% and 50% vs 23%, respectively). At the time of analysis, median overall survival had not been reached, with fewer than 10% of patients experiencing an event. The median duration of follow-up for overall survival was 28 months.

The most common Grade ≥3 adverse reactions (≥10%) in either arm were neutropenia (VenG 56%; GClb 52%), anemia (VenG 8%; GClb 7%), diarrhea (VenG 4%; GClb 1%), and fatigue (VenG 2%; GClb 1%). In the VenG arm, neutropenia led to dose interruption, reduction, and discontinuation of venetoclax in 41%, 13%, and 2% of patients, respectively. The most frequent serious adverse reactions in the VenG arm were febrile neutropenia and pneumonia (5% each). Fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 2% (4/212) of patients in the VenG arm, most often from infection. All Grade adverse reactions of infection and infestations in the VenG arm were also reported (pneumonia, 9%; urinary tract infection, 6%; sepsis, 4%). The rate of TLS with VenG was 1%. All three events of TLS resolved and did not lead to withdrawal from the study; obinutuzumab administration was delayed in two cases in response to the TLS events.

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Also included in this submission are the results from a Phase 1b trial that evaluated safety and efficacy of VenG in patients with relapsed/refractory (R/R) or previously untreated CLL with good performance status and adequate marrow, coagulation, and renal and hepatic function.[2] The study was not limited to patients with coexisting comorbidities. Treatment was given until completion of a 1-year fixed treatment duration; however, patients in the first-line cohort could extend treatment with venetoclax beyond 1 year if there was detectable MRD in the BM or the patient was not in CR. Results from the first-line patient population are provided below.

As of May 21, 2018, 32 first-line patients were enrolled. Venetoclax treatment duration was 371 days (range, 314-883). The most prevalent Grade 3/4 AEs were neutropenia (53%), thrombocytopenia (22%) and febrile neutropenia (13%). One incidence of laboratory TLS occurred in a first-line patient after obinutuzumab and before initiation of venetoclax. No clinical TLS was reported. The ORR was 100% for

the entire first-line population, which included patients with cytogenetic abnormalities. The CR/complete response with incomplete bone marrow recovery (CRi) rate was 78%. In the peripheral blood, 91% (29/32) of first-line patients achieved MRD negativity (<1 CLL cell/$10^4$ leukocytes) ≥3 months after completion of obinutuzumab. The rate of MRD negativity was maintained at 72% ≥3 months after end of all treatment. MRD negativity in the bone marrow was achieved in 78% of patients. After a median follow-up of 26.7 months (range, 16-39) in first-line patients, estimated 24-month PFS was 90.6% (95% CI: 80.5 to100.0).

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In summary, venetoclax in combination with obinutuzumab has shown statistically significant improvements in PFS and depth of remission (CR and MRD negativity) in comparison to GClb while maintaining a safety profile consistent with both compounds. Most patients were able to complete the scheduled 12 months of therapy and remain progression free up to 12 months after stopping therapy. A complementary phase 1b dataset in patients irrespective of fitness status also showed 2-year PFS rates of 90.6%.

The following cited prescribing information and published article are submitted in support of this proposed amendment:


1. Venclexta® [package insert]. Chicago, IL: AbbVie, Inc., 2019.
2. Flinn IW, Gribben JG, Dyer MJS, et al. Phase 1b study of venetoclax-obinutuzumab in previously untreated and relapsed/refractory chronic lymphocytic leukemia. *Blood*. 2019; pii: blood-2019-01-896290; DOI: 10.1182/blood-2019-01-896290. [Epub ahead of print]


Respectfully submitted,


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