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

On behalf of AbbVie and Genentech, I respectfully submit to the NCCN Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) Guideline Panel the published data for Venclexta® (venetoclax) in combination with Gazyva® (obinutuzumab) (VenG) compared with standard of care for first-line (1L) treatment of patients with CLL.

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.

On May 16, 2019, we submitted the recently approved US prescribing information with the expanded indication for Venclexta in the first-line CLL/SLL setting, along with the publication of 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.[1,2] Herein we provide additional clinical data now published in the New England Journal of Medicine and presented at the 2019 ASCO Annual Meeting and request your consideration of the following changes to the NCCN CLL/SLL guidelines.

Specific Change Request #1

Consider a recommendation of venetoclax plus obinutuzumab as a first-line, preferred, regimen for CLL/SLL without del (17p)/TP53 mutation in patients <65 y without significant comorbidities.

Rationale: In a Phase 3 randomized, controlled trial evaluating VenG versus obinutuzumab plus chlorambucil (GClb) for the treatment of previously untreated patients with CLL and coexisting medical conditions, the primary endpoint was investigator (INV)-assessed progression free survival (PFS).[3,4] Secondary endpoints were analyzed using a hierarchical methodology and included: independent review committee (IRC)-assessed PFS as well as minimal residual disease (MRD) in the peripheral blood (PB) and bone marrow (BM), overall and complete response rates, MRD negativity (defined as <1 CLL cell/10^4 leukocytes) in complete response in PB and BM (all assessed 3 months after treatment completion) and overall survival.[4]

Baseline characteristics were similar between study arms.[3] Although the inclusion criteria specified 1L CLL patients with comorbidities, 15% and 20% of patients in the VenG and GClb arms, respectively, had a total Cumulative Illness Rating Scale (CIRS) score ≤6 and a median estimated creatinine clearance of 65.2 mL/min and 67.5 mL/min.[4] In addition, all patients with the exception of one, had an ECOG performance status score between 0-2 (87% of patients in the VenG arm had a baseline performance status of 0-1).[3] Patients in the VenG and GClb arms included 14% and 13.7% with *TP53* deletion and/or mutation, 60.5% and 59.1% with unmutated IGHV, and 8.5% and 7.3% with del(17p), respectively. At this analysis, all patients were off treatment for a median duration of 17.1 months (range, 0-30.4) and 17.9 months (range, 0-30.2), for the VenG and GClb arms, respectively.[3] Median relative dose intensity was 95.1% for venetoclax, 95.4% for chlorambucil and 100% for obinutuzumab.

INV-assessed 24-month PFS was significantly improved in the VenG arm versus the GClb arm (Hazard ratio [HR] 0.35; 95% confidence interval [CI]: 0.23 to 0.53, P<0.001) which was consistent with IRC-assessed 24-month PFS (HR 0.33; 95% CI: 0.22 to 0.51, P<0.001). Improvement in INV-assessed PFS was also consistently seen across pre-specified major prognostic subgroups, including age (<75 years; HR 0.28; 95% CI: 0.16-0.48), *TP53* deletion and/or mutation (HR 0.31; 95% CI: 0.13-0.76) and unmutated IGHV (HR 0.22; 95% CI: 0.12-0.38).[4] Secondary endpoints of IRC-assessed PFS, MRD, and overall and CR rates met the prespecified hierarchical criteria for statistical significance. MRD negativity in complete response (3 months after treatment completion) in both the PB and BM was significantly higher with VenG than with GClb (PB: 42.1% vs. 14.4% [P<0.001]; BM: 33.8% vs. 10.6% [P<0.001], respectively). Using a cutoff of 10^{-6}, MRD negativity rates in PB by next-generation sequencing (NGS) 3 months after treatment completion, were 42% in the VenG arm and 7% in the GClb arm.[5] Depth of response is further demonstrated in the time to next anti-leukemic treatment time plot (Figure).[4]

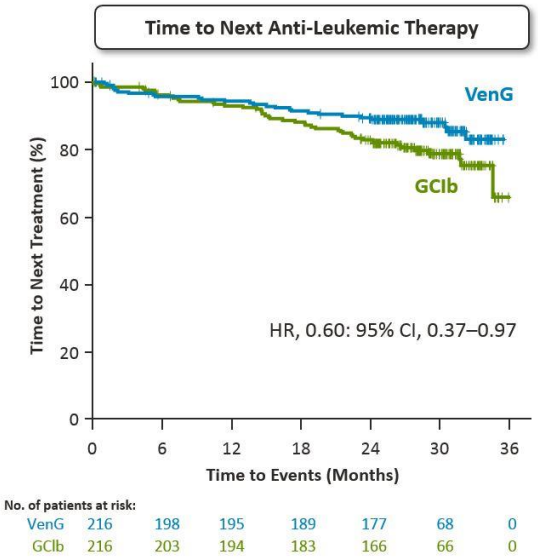

Figure. Time to Next Anti-Leukemic Treatment[4]

Similar to the US prescribing information, the most common Grade 3 or 4 adverse events (AE) reported in the publication across both arms were neutropenia (VenG 52.8%; GClb 48.1%), thrombocytopenia (VenG 13.7%; GClb 15.0%), and infusion-related reactions (VenG 9.0%; GClb 10.3%).[3] Fatal AEs were reported in 2% of patients in each arm during study treatment and 5% (11/212) and 2% (4/214) of patients after completion of treatment in the VenG and GClb arms, respectively. There were no reports of clinical TLS. Laboratory TLS occurred in 3 and 5 patients in the VenG and GClb arms, respectively; all 3 TLS events in the VenG arm occurred during the initial treatment with obinutuzumab, before initiation of venetoclax.

Specific Change Request #2

Consider an update of the dosing and administration recommendations for venetoclax.

Rationale: To provide additional details that characterize the differences in dosing regimens and duration of therapy between venetoclax monotherapy and venetoclax in combination with rituximab and obinutuzumab as follows:

- **Addition of the following new footnote on CSLL-D (4 of 6):** **"[t]** *Venetoclax in combination with an anti-CD20 (rituximab or obinutuzumab) may be given as fixed duration therapy",* referenced in the following areas of the guideline:
    - CSLL-D (1 of 6), CLL/SLL without del (17p)/*TP53* mutation 1L therapy:

      Venetoclax [e,f,t] + obinutuzumab
    - CSLL-D (2 of 6), CLL/SLL without del (17p)/*TP53* mutation R/R therapy:

      Venetoclax [e,f,t] + rituximab
    - CSLL-D (3 of 6), CLL/SLL with del(17p)/*TP53* mutation:

      1L therapy – Venetoclax [e,f,t] + obinutuzumab
      R/R therapy – Venetoclax [e,f,t] + rituximab

- Update of CSLL-F (3 of 4) to reflect dosing and duration of therapy for venetoclax in combination with an anti-CD20 (rituximab and obinutuzumab):
    - **Dosage:** *The recommended dose of venetoclax is given for a total of 12 months when used as first-line therapy in combination with obinutuzumab; for a total of 2 years when used as relapsed/refractory therapy in combination with rituximab; and until disease progression or unacceptable toxicity as single agent relapsed/refractory therapy.*
    - **Detail for combination regimens:**

      Venetoclax in combination with obinutuzumab
      Obinutuzumab administration initiated prior to starting venetoclax. Start obinutuzumab on Cycle 1 Day 1 at 1000mg dose according to recommended dosing in prescribing information and continue for 6 cycles. On Cycle 1 Day 22, start venetoclax according to the 5-week ramp-up schedule. After completing the ramp-up schedule on Cycle 2 Day 28, continue venetoclax 400 mg once daily for a total of 12 months (includes duration of 5-week ramp-up).

      Venetoclax in combination with rituximab
      Initiate venetoclax according to a 5-week ramp-up schedule. Following initial 5-week ramp-up, administer venetoclax at 400mg once daily in combination with rituximab given on Day 1 of each 28-day cycle for 6 cycles. After completion of venetoclax plus rituximab combination therapy, continue venetoclax at 400mg once daily for a total of 2 years from Cycle 1 Day 1.

References

The following cited references are submitted in support of these proposed amendments:

1. 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].
2. Venclexta® [package insert]. Chicago, IL: AbbVie, Inc., 2019.
3. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019; DOI: 10.1056/NEJMoa1815281.
4. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions [supplement]. *N Engl J Med*. 2019; DOI: 10.1056/NEJMoa1815281.
5. Fischer K, Al-Sawaf O, Bahlo J, et al. Effect of fixed-duration venetoclax plus obinutuzumab (VenG) on progression-free survival (PFS), and rates and duration of minimal residual disease negativity (MRD–) in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) and comorbidities. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4, 2019; Chicago, IL. Oral presentation.

Respectfully submitted,

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