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NCCN Guidelines® Panel: Acute Myeloid Leukemia

On behalf of AbbVie and Genentech, I respectfully request the NCCN Acute Myeloid Leukemia (AML) Guidelines Panel to consider the enclosed, recently updated and published data for Venclexta® (venetoclax) in combination with azacytidine (AZA), decitabine (DEC) and low dose cytarabine (LDAC) in newly diagnosed AML patients ineligible for intensive chemotherapy (IC). This submission contains extended safety and efficacy data for venetoclax in combination with AZA and LDAC from the VIALE-A and VIALE-C trials, respectively, extended data from Phase 1b and Phase 1/2 studies of venetoclax in combination with hypomethylating agents (HMAs) and LDAC; and a summary of real-world data for venetoclax and HMAs in newly diagnosed patients with AML ineligible for IC.

#### **Specific changes recommended within the NCCN Guidelines**

- Consider inclusion of venetoclax + HMAs (AZA or DEC) as a category 1 preferred regimen for patients with newly diagnosed AML ≥60 years of age who are not candidates for intensive remission induction therapy or decliners (AML-6).

#### **FDA Clearance:**

Venclexta® (venetoclax) is a BCL-2 inhibitor indicated in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly-diagnosed acute AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.<sup>1</sup> This indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

#### **Rationale:**

The results of a phase 3, double-blinded, randomized study (VIALE-A) in treatment-naïve patients with confirmed AML who were ineligible for IC comparing the therapy with Ven + AZA vs AZA + placebo (PBO) were recently presented at the European Hematology Association (EHA) Annual Congress.<sup>2</sup> The primary endpoint of the study was overall survival (OS). Key secondary endpoints included rates of complete remission (CR), CR + CR with incomplete count recovery (CR/CRi), CR/CRi by initiation of cycle 2, CR + CR with incomplete hematologic recovery (CR/CRh), transfusion independence (TI), outcomes by molecular subgroups (including IDH1/2 and FLT3), and safety.

Patients were randomized 2:1 to receive treatment with Ven + AZA or AZA + PBO. In total, 286 patients received 400 mg Ven in combination with AZA and 145 patients received AZA + PBO. As of the data cut-off date of January 4, 2020, median follow-up was 20.5 months and median duration of treatment for Ven + AZA and AZA + PBO was 17.5 and 13.4 month, respectively.

Treatment with Ven + AZA resulted in statistically significant and clinically meaningful improvement in OS vs AZA + PBO. The median OS was 14.7 months in Ven + AZA and 9.6 months in AZA + PBO (HR: 0.66, 95% CI: 0.52–0.85,  $P < 0.001$ ) respectively, representing a 34% reduction in risk of death. Response rates of CR observed for patients treated with Ven + AZA vs AZA + PBO were 37% and 17.9%, respectively. Treatment with Ven + AZA also led to significant improvement in response rates: CR/CRi rates in Ven + AZA/AZA + PBO were 66% and 28% ( $P < 0.001$ ) respectively. A statistically significant and clinically meaningful increase in CR/CRh rate was achieved in 65% of Ven + AZA treated patients compared to 23% in PBO + AZA treated patients. By start of cycle 2, CR/CRi was achieved in 43% of Ven + AZA patients and only in 7.6% of PBO + AZA patients. Duration of response, measured as CR/CRh, in the Ven + AZA arm was maintained for a median of 17.8 months compared to 13.9 months in patients treated with AZA + PBO.

At baseline, genetic mutations of IDH1/2 and FLT3 were observed in the Ven + AZA (25% and 14%) and AZA + PBO (22% and 20%) arms. Overall survival favored patients treated in the Ven + AZA arm compared with AZA + PBO arm in patients with IDH1/2 (HR 0.3, 95% CI 0.2-0.6) and FLT3 (HR 0.66, 95% CI 0.35-0.1.26) mutations at baseline. In addition, response rates of CR/CRi were 75%/72% (VEN + AZA) vs. 11%/36% (AZA + PBO) for patients with IDH1/2 and FLT3 mutations, respectively.

The rate of TI was higher in the Ven + AZA arm compared with AZA + PBO with statistical significance observed for RBC and platelet transfusion; 60%/69% vs 35%/50% ( $P < 0.001$ ). Grade  $\geq 3$  hematological adverse events included (Ven + AZA/AZA + PBO) thrombocytopenia (45%/38%), neutropenia (45%/29%), febrile neutropenia (42%/19%), anemia (26%/20%) and leukopenia (21%/12%).

Also, included in this submission are the results of the VIALE-C phase 3 study in treatment-naïve patients with confirmed AML who were ineligible for standard induction therapy.<sup>3</sup> A total of 143 patients received 600 mg Ven (after an initial 4-day ramp-up schedule) in combination with LDAC and 68 patients were treated with LDAC + PBO. As of the data cut-off of February 15, 2019, for the initial analysis, median time on study treatment was 3.9 and 1.7 months and median follow up was 12 months in both groups. Patients received a median of 4 cycles in the Ven + LDAC arm vs 2 cycles in the LDAC + PBO arm.

The median OS was 7.2 months in Ven + LDAC and 4.1 months in LDAC + PBO (HR: 0.75, 95% CI: 0.52-1.07,  $P = 0.11$ ). This represented a 25% reduction in risk of death. Although the initial median OS was not statistically significant, an unplanned analysis at 6 months follow up provided a median OS of 8.4 months in the Ven + LDAC group compared with 4.1 months in the LDAC + PBO group (HR 0.70; 95% CI 0.50–0.98;  $p = 0.04$ ), representing a 30% reduction in the risk of death. The CR + CRi rates were significantly higher in the Ven + LDAC group at 48% vs 13% in LDAC + PBO group ( $P < 0.001$ ). Rates of TI were significantly higher for patients treated with Ven + LDAC, with 37% (95% CI 29–46) of patients achieving RBC and platelet TI, compared to 16% (95% CI 8–27) for those treated with LDAC + PBO. Grade  $\geq 3$  hematologic adverse events occurred in 78% of patients treated with Ven + LDAC and 74% in patients in the LDAC + PBO group. Hematologic adverse events for (Ven + AZA/AZA + PBO) included neutropenia (49%/18%); thrombocytopenia (46%/38%), febrile neutropenia (32%/29%), and anemia (27%/22%).<sup>4</sup>

Additionally, recently published long-term follow-up of the phase 1/2 (M14-387) study evaluating Ven + LDAC in newly-diagnosed AML patients ineligible for IC showed that with a median treatment duration of 4.2 months (range 0.8-14.9) the CR/CRi rate was 54% and median OS was 9.7 months (95% CI 5.7, 14.0).<sup>5</sup> A longer median OS was observed in patients who had mutations in NPM1 or IDH1/2 (not reached and 15.9 months, respectively).

Recent data from phase 1b (M14-358) and phase 1b/2 (M14-387) studies evaluated timing of response on Ven in combination with AZA or DEC (AZA/DEC) and LDAC is also included.<sup>6</sup> Greater than 90% of CR/CRi responses occurred within 4 cycles of Ven + AZA/DEC and within 6 cycles with Ven + LDAC. Of the 197 patients evaluated, 42% (n=83) achieved CR/CRi in  $\leq 2$  cycles and 22% (n=44) achieved CR/CRi in  $>2$  cycles. Patients with baseline IDH1/2 and NPM1 mutations were more likely to achieve CR/CRi in  $\leq 2$  cycles with 67% (29/43) and 62% (16/26) with baseline IDH1/2 and NPM1 mutations achieved CR/CRi in  $\leq 2$  cycles of treatment respectively.

Recently published real-world studies evaluated clinical outcomes, hospitalization rates, and transfusion dependence (TD) in AML patients  $\geq 66$  years receiving 1L HMA monotherapy demonstrated significant unmet need for therapies that improve patient outcomes and reduce transfusion dependence in this patient population.<sup>7,8,9</sup> In a SEER-Medicare analysis, 2,263 AML patients  $\geq 66$  years were evaluated.<sup>7</sup> The cohort of HMA-treated patients had a median age of 77 (interquartile range: 72-82) years and received a median of 3 (IQR: 1-6) cycles of HMA with 42% of the cohort completing  $\geq 4$  cycles of therapy.<sup>7</sup> Among those that were RBC transfusion dependent (TD) prior to HMA initiation, TI was observed in 33%. In the subset of patients who received  $\geq 4$  cycles of treatment, conversion from RBC TD at baseline to TI was 57%.

An observational real-world study of AML patients  $\geq 60$  years included 378 patients who were treated with low intensity therapy in the community setting.<sup>8</sup> Most patients received 1L HMA monotherapy with AZA, (57.9%) or DEC (25.9%) and the median duration of therapy was 2.9 (range: 0.0, 46.9) and 2.5 (range: 0.1, 26.4) months, respectively. In the HMA cohort, 84% of patients received at least one transfusion prior to treatment initiation. During treatment, patients had a median of 4 transfusions of RBC or platelet.<sup>7</sup> Median (95% CI) OS, time-to-treatment failure, and PFS in the AZA and DEC cohorts were 7.5 (5.7, 9.6) and 7.3 (4.8, 8.8) months; 3.4 (2.8, 4.4) and 3.7 (2.4, 5.2) months, and 6.7 (5.0, 8.0) and 5.7 (3.4, 7.4) months, respectively. Hospitalization rates were similar between AZA (79.9%) and DEC cohorts (83.7%) and the rates of hospitalization  $> 2$  days duration were 64.4% and 66.3%, respectively. Median (range) duration of hospitalization was 6.5 (3.0-34.0) and 7 (3.0-26.0) days in the AZA and DEC cohorts.

In another recent observational study of 1,776 AML patients  $\geq 60$  years receiving therapy with AZA or DEC, 57% (n=1,004) were RBC TD and 22% (n=390) were platelet TD at baseline.<sup>9</sup> Within the first month of treatment initiation, 76% and 45% of the cohort required  $\geq 1$  transfusion of RBC and platelets respectively. The proportion of patients requiring transfusions decreased over the course of treatment and stabilized 6 months after treatment initiation.

These recently published studies describe real world experience with HMA monotherapy in older AML patients demonstrated that TD persists through most of the duration of treatment with HMAs and patients experience high rates of hospitalization adding to the overall burden of AML in older patients.<sup>7,8,9</sup>

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

1. Venclexta® [package insert]. Chicago, IL: AbbVie, Inc., 2019.
2. DiNardo CD, Jonas BA, Pullarkat V, et al. A randomized, double-blind, placebo-controlled study of venetoclax with azacitidine vs azacitidine in treatment-naïve patients with acute myeloid leukemia ineligible for intensive therapy: VIALE-A. Presented at the European Hematology Association (EHA) 25<sup>th</sup> Annual Meeting; June 14, 2020; Virtual Scientific Program. Oral presentation LB2601.
3. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for patients with untreated AML ineligible for intensive chemotherapy: phase 3 randomized placebo-controlled trial. Blood. 2020. <https://doi.org/10.1182/blood.2020004856>. [Epub ahead of print].
4. Wei, AH, Montesinos P, Ivanov V, et al. A phase 3 study of venetoclax plus low-dose cytarabine in previously untreated older patients with acute myeloid leukemia (VIALE-C): a 6-month update. Poster presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020; Virtual Scientific Program. Poster 7511.
5. Wei AH, Strickland S, Hou JZ, et al. Long-term follow-up of a phase 1/2 study of venetoclax plus low-dose cytarabine in previously untreated older adults with acute myeloid leukemia. Poster presented at the European Hematology Association (EHA) 25<sup>th</sup> Annual Meeting; June 11-14, 2020; Virtual Scientific Program. Poster EP554.
6. Jonas BA, DiNardo CD, Pratz K, et al. Timing of Response to venetoclax combination treatment in older patients with acute myeloid leukemia. Poster presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020; Virtual Scientific Program. Poster 7531.
7. Shallis R, Wang R, Wang X, et al. Clinical outcomes of older patients with acute myeloid leukemia (AML) receiving hypomethylating agents: a large population-based study in the united states. Poster presented at the European Hematology Association (EHA) 25<sup>th</sup> Annual Meeting; June 11-14, 2020; Virtual Scientific Program. Poster EP534.
8. Lyons R, Potluri J, Bui C, et al. Treatment outcomes and healthcare resource utilization (HRU) among patients with acute myeloid leukemia (AML) ineligible for intensive chemotherapy in US community oncology setting. Abstract presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020; Virtual Scientific Program. Abstract E19513.
9. Le Blanc TW, Seetasith A, Choi M, et al. Transfusion burden on older patients with acute myeloid leukemia receiving low-intensity treatments. Poster presented at the European Hematology Association (EHA) 25<sup>th</sup> Annual Meeting; June 11-14, 2020; Virtual Scientific Program. Poster EP1739.

Respectfully submitted,



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