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 NCCN Guidelines® Panel: Acute Myeloid Leukemia

On behalf of AbbVie and Genentech, I respectfully submit to the NCCN Acute Myeloid Leukemia (AML) Guidelines Panel the updated and published data for Venclaxta® (venetoclax, Ven) in patients with AML. On November 21, 2018, FDA expanded the label and approved Venclaxta® in combination with azacitidine (Aza) or decitabine (Dec) or low-dose cytarabine (LDAC) for the treatment of newly-diagnosed AML in adults who are age 75 or older or who have comorbidities that preclude use of intensive induction chemotherapy. This was an accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

On November 21, 2018, we submitted the ASH 2018 online abstract data from the Phase 1b (Ven + Aza or Ven + Dec) and Phase 1/2 (Ven + LDAC) studies in newly-diagnosed patients with AML ineligible for intensive chemotherapy.^{1,6} Herein we provide the longer-term follow up and mutational subgroup data from these two studies^{2,7,8} and request the following changes for your consideration within the NCCN AML guidelines.

Specific changes: Please find below proposed changes for your consideration

Specific section	Specific change
AML-13	<p><u>Specific Change 1:</u> Please consider including the combination of venetoclax with azacitidine, decitabine or low-dose cytarabine as a recommendation for treatment induction in patients ineligible for intensive remission induction therapy who have <i>IDH1</i>, <i>IDH2</i> or <i>FLT3</i> mutations</p> <p><u>Specific Change 2:</u> Please consider recommending the combination of venetoclax with azacitidine, decitabine or low-dose cytarabine as a “Preferred” regimen within all Treatment Strategies for AML patients ≥60 years who are not a candidate for intensive remission induction therapy or decliners.</p>
AML-16	<p><u>Specific Change 3:</u> In the section “Marrow to document remission status upon hematologic recovery”, please consider response assessment footnote specific to venetoclax treatment that states: “Perform bone marrow to assess response starting at the end of cycle 1 as median time to first response with venetoclax was approximately 1-2 months (range: < 1 month to 14.9 months).”</p>

FDA Clearance: On November 21, 2018, under accelerated approval, FDA approved Ven in combination with Aza or Dec or LDAC for the treatment of newly-diagnosed AML in adults who are age 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy.

Venetoclax Phase 1b/2 Studies in AML

The Phase 1b (M14-358) and Phase 1/2 (M14-387) studies evaluated Ven + Aza, Ven + Dec or Ven + LDAC in patients with newly-diagnosed AML who were ineligible for intensive induction chemotherapy.^{2,7}

In M14-358 study, a total of 115 patients received 400 mg Ven in combination with either Aza (n = 84) or Dec (n = 31) (Data cut-off date Aug 31, 2018). In M14-387 study, a total of 82 patients were treated with 600 mg Ven + LDAC (efficacy data cut-off date November 8, 2017; safety data cut-off date January 30, 2018).

➤ **Rationale for Specific Change 1**

Ven + Aza, Ven + Dec or Ven + LDAC demonstrated efficacy across varied mutational subgroups in patients with newly-diagnosed AML who are ineligible for intensive induction chemotherapy. Efficacy of these combinations in the overall population and the *IDH1/2* and *FLT3* mutational subgroups is represented in the figure below.

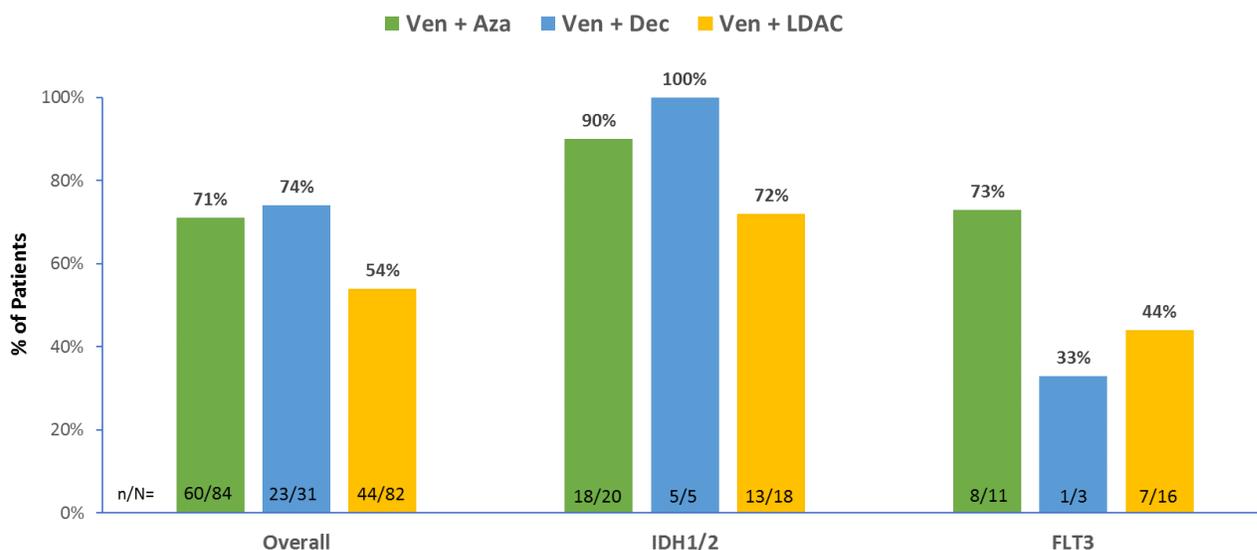


Figure. CR/CRi rates in Overall Population and Across *IDH1/2* and *FLT3* Mutational Subgroups^{2,8}

Abbreviations: CR, complete remission; CRi, complete remission with incomplete blood count recovery

Median overall survival (OS) is also available for *IDH1/2* and *FLT3* mutational subgroups. In the Ven + LDAC study, median OS was 19.4 months (95% CI, 5.1–not reached [NR]) for patients with *IDH1/2* mutation (n=18) and 5.6 months (95% CI, 3.0–14.3) for patients with *FLT3* mutation (n=16).⁸ For the Ven + HMA study, during an earlier data cut-off date of July 7, 2017 where patients were treated at 400 mg, 800 mg or 1200 mg Ven with Aza or Dec (N=145), the median OS was 24.4 months (95% CI, 12.3–NR) for patients with *IDH1/2* mutation (n=35) and was NR (95% CI, 8–NR) for patients with *FLT3* mutation (n=18).³

➤ **Rationale for Specific Change 2**

At the most recent data cut, rates of CR+CRi in the overall population treated with Ven + Aza, Ven + Dec, or Ven + LDAC were 71%, 74%, and 54%, respectively.^{2,7} For the Ven + Aza group, the median follow-up time was 14.9 months (range, 0.4–42.0), median OS was 16.9 months (95% CI, 11.3–NR), and 12-month no event rate for duration of response (DOR) after achieving CR/CRi was 69% (95% CI, 52%–80%).² For Ven + Dec group, the median follow-up time was 16.2 months (range, 0.7–42.7), median OS was 16.2 months (95% CI, 9.1–27.8), and 12-month no event rate for DOR after achieving CR/CRi was 57% (95% CI, 32%–76%). In the Ven + LDAC study, median OS was 10.1 months (95% CI, 5.7–14.2) and median DOR was 8.1 months (95% CI, 5.3–14.9).⁷

Additionally, please see “Rationale for Specific Change 1” for the efficacy data in the *IDH1/2* and *FLT3* mutational subgroups.

Based on these results, please consider recommending the combination of venetoclax with azacitidine, decitabine or low-dose cytarabine as a “Preferred” regimen within all Treatment Strategies for AML patients ≥60 years who are not a candidate for intensive remission induction therapy or decliners.

➤ **Rationale for Specific Change 3**

Disease status is used to determine management of clinically significant cytopenia for AML patients treated with Ven in combination with Aza, Dec, or LDAC (Table 6, Venclexta PI).¹⁰ Since median time to CR was 1.2 months (range, 0.7–5.5) in Ven + Aza group,² 1.9 months (range, 0.9–4.6) in Ven + Dec group,² and 1.4 months (range, 0.8–14.9) for Ven + LDAC group,⁷ response assessment should be performed earlier since appropriate management of cytopenias is guided by response. Response assessment for M14-358 study was performed using bone marrow aspirate and biopsy at the end of Cycle 1 and every 3 cycles thereafter.⁴ Bone marrow assessments in the M14-387 study were performed after Cycles 1 and 3, and then every 3 cycles thereafter.⁷

Ongoing Phase 3 Studies

1. A randomized, double-blind, placebo-controlled, Phase 3 study is evaluating the efficacy and safety of 400 mg Ven + Aza versus placebo + Aza in newly-diagnosed patients with AML who are ≥18 years and are ineligible for intensive chemotherapy.⁵
2. A randomized, double-blind, placebo-controlled, Phase 3 study is evaluating the efficacy and safety of 600 mg Ven + LDAC versus placebo + LDAC in newly diagnosed AML who are ≥18 years and are ineligible for intensive chemotherapy.⁹

FDA Approved Indications and Uses of Venetoclax:

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Ven is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy.

AML

Ven is indicated in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly -diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

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.

For complete information about venetoclax, please refer to the US prescribing information available at: www.rxabbvie.com.

Respectfully submitted,

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