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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 enclosed, updated and published data in patients with AML and the US Prescribing Information for Venclaxta® (venetoclax). On November 21, 2018, FDA expanded the label and approved venetoclax (Ven) 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 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.

On July 12, 2018, we submitted to the NCCN AML Guidelines Panel the Ven data in AML presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting¹ and 2017 American Society of Hematology (ASH) Annual Meeting.⁶ Herein we provide the updated data with longer term follow-up from abstracts published online at the 2018 ASH Annual Meeting website.^{2,7} Following the ASH 2018 oral presentations, we will submit further updated data to the panel.

Specific changes recommended within the NCCN Guidelines

- Please include the combination of venetoclax with azacitidine, decitabine or low-dose cytarabine as a preferred recommendation for treatment induction in patients ineligible for intensive remission induction therapy (AML-8, AML-12 and relevant discussion sections)

1. Ven in Combination with Aza or Dec

Specific Changes: As mentioned above.

FDA Clearance: On November 21, 2018, FDA approved Ven in combination with Aza or Dec 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.

Rationale: Treatment with Ven + Aza or Ven + Dec led to high rates of rapid, deep, and durable responses in patients with newly-diagnosed AML who are ineligible for intensive induction chemotherapy.² Thus Ven in combination with hypomethylating agents (HMAs) may provide an effective therapeutic option for these patients.

DiNardo et al. recently published on a Phase 1b study of Ven in combination with Aza or Dec in patients with newly-diagnosed AML who are ineligible for intensive induction chemotherapy due to comorbidities and age.^{3,4} All patients were hospitalized and received tumor lysis syndrome (TLS) prophylaxis during the Ven dose ramp up in Cycle 1. No events of TLS were observed. Additionally, patients were allowed in the study if they had a white blood cell count < 25 × 10⁹/L (hydroxyurea or leukapheresis were permitted to meet this criterion).

Based on the safety and efficacy data from the dose escalation stage, 400 mg dose of Ven was studied in combination with Aza or Dec in the expansion stage; updated results as of data cut-off date of December 22, 2017 are provided herein.² Ven was administered daily in a 3 day ramp-up schedule from 100 to 200 to 400 mg and coadministered with either 20 mg/m² intravenous (IV) Dec on days 1-5 or 75 mg/m² IV or subcutaneous (SC) Aza on days 1-7 of each 28 day cycle.

A total of 115 patients received 400 mg Ven in combination with either Aza (n = 84) or Dec (n = 31). Key baseline characteristics for patients in Ven + Aza and Ven + Dec groups, respectively, were as follows - median age, 75 (range: 61–90) and 72 (range: 65–86) years; secondary AML, 25% and 29% of patients; poor cytogenetic risk, 39% and 48% of patients; transfusion dependence for red blood cells (RBC) or platelets within 8 weeks prior to Ven treatment, 64% (54/84) and 74% (23/31) of patients.

Median time on study treatment was 6.4 and 5.7 months, and median follow up was 8.2 (range: 0.4–35.5) and 16.2 (range: 0.7–36.7) months for Ven + Aza and Ven + Dec groups, respectively. Efficacy results for Ven + Aza and Ven + Dec groups, respectively, were as follows: 70% and 74% of patients achieved CR+CR with incomplete blood count recovery (CR+CRi), 67% and 71% patients achieved CR+CR with partial hematologic recovery (CR+CRh), median time to CR/CRi was 1.2 and 1.9 months, duration of CR+CRi was 68% and 57%, duration of CR+CRh was 69% and 55%, and median overall survival (OS) was 14.9 and 16.2 months. Across both treatment groups, 52% (40/77) of patients who were transfusion dependent at baseline achieved transfusion independence from both RBC and platelets, defined as not receiving RBC or platelet transfusions for ≥56 days. Among patients with CR/CRi, 45% achieved minimal residual disease (MRD) response (i.e. < 10⁻³ leukemic cells). Patients who received Ven dose reduction with CYP3A inhibitors had similar responses compared to those without dose reduction.

Ven in combination with Aza or Dec demonstrated similar efficacy profiles across varied cytogenetic and mutational profiles. CR/CRi rates for Ven + Aza and Ven + Dec groups, respectively, in these subgroups were as follows: 74% (37/50) and 69% (11/16) for patients with intermediate risk cytogenetics, 67% (22/33) and 80% (12/15) for patients with poor risk cytogenetics, 65% (13/20) and 86% (6/7) for patients with *TP53* mutation, 90% (18/20) and 100% (5/5) with *IDH1/2* mutation, 64% (7/11) and 33% (1/3) with *FLT3* mutation, and 71% (10/14) and 100% (3/3) with *NPM1* mutation.

Most common grade ≥3 adverse events were febrile neutropenia (44%), anemia (28%), pneumonia (25%), thrombocytopenia (22%) and neutropenia (18%). Notably, early mortality was low with 4 deaths occurring within 30 days of start of treatment that may indicate the clinical importance of obtaining an early remission.

An ongoing, 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. Ven in Combination with LDAC

Specific Changes: As mentioned above.

FDA Clearance: On November 21, 2018, FDA approved Ven in combination with 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.

Rationale: Treatment with Ven + LDAC led to high rates of rapid, deep, and durable responses in patients with newly-diagnosed AML who are ineligible for intensive induction chemotherapy.⁷ Thus Ven + LDAC may provide an effective therapeutic option for these patients.

In the Phase 1/2 study of Ven + LDAC in patients with newly-diagnosed AML who are ineligible for intensive induction chemotherapy due to comorbidities and age, the recommended Phase 2 dose of Ven was identified as 600 mg. As of data cut-off date of November 8, 2017, a total of 82 patients were treated with 600 mg Ven + LDAC. Following a protocol amendment, Ven was initiated at 100 mg and dose

escalated over 4 days to reach 600 mg. In subsequent 28 day cycles, Ven was administered at 600 mg on all days. LDAC (20 mg/m² SC daily) was administered on days 1–10 of each cycle. Of 82 patients, 49% had secondary AML, of whom 60% had prior HMA exposure; 60% of patients had intermediate and 32% of patients had poor cytogenetic risk. 65% of patients were transfusion dependent for RBC and 28% for platelets within 8 weeks prior to Ven treatment.

Median time to first response was 1.4 months; 54% and 48% of patients achieved CR/CRi and CR/CRh, respectively. Median duration of CR/CRi was 8.1 months and CR/CRh was 11.0 months. CR/CRi estimate at 24-months was 32% (95% CI = 17% - 48%). Median OS was 10.1 months and 24-month OS estimate was 27% (95% CI = 17% - 38%). Among patients that were RBC or platelet transfusion dependent at baseline, 49% (26/53) and 65% (15/23) achieved transfusion independence, respectively. MRD response (< 10⁻³ leukemic cells) was achieved by 32% of patients with CR/CRi; median OS has not yet been reached for these patients.

Ven + LDAC demonstrated similar efficacy profiles across varied molecular profiles. The rates of CR/CRi for patients with secondary and *de novo* AML were 35% and 71%, and median duration of response were 8.1 and 11.6 months, respectively. Rates of CR/CRi for patients with selected genetic mutations were as follows: 30% (3/10) for *TP53* mutation, 72% (13/18) for *IDH1/2* mutation, 44% (7/16) for *FLT3* mutation, and 89% (8/9) for *NPM1* mutation.

Most common grade ≥3 adverse events were febrile neutropenia (43%), thrombocytopenia (38%), neutropenia (27%), and anemia (27%). Grade 3 laboratory TLS was observed in 2 patients; both of whom achieved the target dose of Ven. 47% of patients received moderate (40%) or strong (7%) CYP3A inhibitors for at least 7 days (mainly azole antifungals) and no relevant differences were observed in the serious adverse event rates.

A randomized, double-blind, placebo-controlled, Phase 3 study is evaluating the efficacy and safety of 600 mg venetoclax + LDAC versus placebo + LDAC in newly diagnosed AML who are ≥18 years and are ineligible for intensive chemotherapy.⁸

Respectfully submitted,

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