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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, published data for Venclexta® (venetoclax) in patients with newly diagnosed AML who are ineligible for intensive chemotherapy. We recently submitted a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) on June 25, 2018 for venetoclax in combination with hypomethylating agents (HMAs) or in combination with low dose cytarabine (LDAC) in this patient population. For more information, please read our press release.

Venetoclax in combination with HMAs (azacitidine [AZA] or decitabine [DEC]) or LDAC has been granted Breakthrough Therapy Designations (BTDs) from the FDA for the treatment of patients with newly diagnosed AML who are ineligible for intensive chemotherapy. Abbvie and Genentech are also conducting phase 3 studies for venetoclax in combination with AZA or LDAC in patients >18 years who are ineligible for intensive chemotherapy.

Specific changes recommended within the NCCN Guidelines

- Please include the combination of venetoclax with 5-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. Venetoclax in Combination with HMAs

Specific Changes: Consider the published Phase 1b clinical safety and efficacy data of venetoclax in combination with HMAs in patients with newly diagnosed AML who are ineligible for intensive chemotherapy.
FDA Clearance: Venetoclax in combination with HMAs is not approved by the FDA for the treatment of AML. On January 29, 2016, the FDA provided BTD status to venetoclax in combination with HMA (AZA or DEC) for the treatment of patients with newly diagnosed AML who are ineligible for intensive chemotherapy.
Rationale: DiNardo et al. recently published on a Phase 1b study of venetoclax in combination with AZA or DEC in patients with newly diagnosed AML who are ineligible for intensive chemotherapy.[1] Based on the safety and efficacy data in the dose escalation stage of the study, 400 mg and 800 mg venetoclax doses in combination with the HMAs were studied in the expansion stage. At the 2018 American Society of Clinical Oncology Annual Meeting, updated safety and efficacy data were reported for 145 patients treated with venetoclax 400 mg or 800 mg in combination with AZA (n=72) or DEC (n=73).[2] We continue to collect additional data from this study with longer term follow-up.

As of data cut-off date of July 7, 2017, the median time on study for these 145 patients was 8.9 months (range, 0.2-31.7 months) and median duration of follow up was 15.6 months; the CR+CRi rate was 67%. The CR+CRi rates for venetoclax 400 mg + AZA (n=29) and venetoclax 400 mg + DEC (n=31) arms were 76% and 71%, respectively. Median duration of response (DOR) after CR/CRi was not reached (NR) (95% confidence interval [CI] = 5.6-NR) for the venetoclax 400 mg + AZA arm and was 12.5 months (95% CI = 5.1-NR) for the venetoclax 400 mg + DEC arm. Median overall survival (OS) for patients

receiving venetoclax 400 mg plus AZA or DEC has not been reached yet; median OS for all patients (N=145) was 17.5 months (95% CI = 12.3-NR) with approximately 50% survival after 1 year.

Venetoclax with AZA or DEC showed similar efficacy profiles across adverse karyotypes and varied patient profiles. In patients with intermediate risk (n=74) and poor risk (n=71) cytogenetics, the CR+CRi rates were 74% and 59%, respectively. For patients with secondary AML (n=36), the CR+CRi rate was 67%, same as those with de novo AML (n=109).

Overall, the safety profile was similar between AZA and DEC arms at respective doses. For the overall study population (N=145), adverse events (AEs) of any grade occurring in ≥30% of patients included: nausea, diarrhea, constipation, febrile neutropenia, fatigue, hypokalemia, decreased appetite, decreased white blood cell (WBC) count, vomiting, and decreased platelet count. Grade 3/4 AEs (≥30%) included febrile neutropenia and decreased WBC count. Febrile neutropenia was the serious AE reported in ≥30% of the patients. No events of laboratory or clinical tumor lysis syndrome (TLS) were observed. Deaths were reported in 3% (n=5) of patients ≤30 days after the start of venetoclax and 8% (n=11) of patients ≤60 days after the start of venetoclax.

Minimal residual status (MRD) status (defined as $<10^{-3}$ leukemic cells at any measurement as detected by multicolor flow cytometry in bone marrow biopsies) was determined in patients who achieved a CR/CRi. In the overall population, 29% patients achieved MRD negative status. For the venetoclax 400 mg + AZA arm and venetoclax 400 mg + DEC arm, MRD negative rates were 45% and 32%, respectively. Pooled data on MRD status from the venetoclax + HMA and venetoclax + LDAC studies was recently presented by Strickland et al. at the European Hematology Association (EHA) 2018 conference.[3]

An ongoing, randomized, double-blind, placebo-controlled, Phase 3 study is evaluating the efficacy and safety of venetoclax co-administered with AZA versus placebo with AZA in newly diagnosed patients with AML who are ≥18 years and are ineligible for intensive cehmotherapy.[4] Based on the efficacy and safety data from the Phase 1b study above, patients will receive venetoclax 400 mg or placebo with AZA.

2. Venetoclax in Combination with LDAC

Specific Changes: Consider the published Phase 1/2 clinical safety and efficacy data of venetoclax in combination with LDAC in patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

FDA Clearance: Venetoclax in combination with LDAC is not approved by the FDA for the treatment of AML. On July 21, 2017, the FDA provided BTD status to venetoclax in combination with LDAC for newly diagnosed patients with AML who are ineligible for intensive chemotherapy.

Rationale: Wei et al. presented on a Phase I/2 study of venetoclax in combination with LDAC at the 2017 American Society of Hematology Annual Meeting.[5] The recommended Phase 2 dose of venetoclax was identified as 600 mg in Phase 1 portion of the study. Long-term survival outcomes (median follow-up >1 year) were reported for 61 patients with newly diagnosed AML (n=8 in Phase 1, n=53 in Phase 2) who are ineligible for intensive chemotherapy and receiving 600 mg of venetoclax in combination with LDAC. We continue to collect additional data from this study with longer term follow-up.

As of data cut-off date of August 15, 2017, the CR+CRi rate in the 61 patients was 62%; median duration of CR/CRi was 13.2 months (95% CI = 5.6-15.0). Median time to response was 1 month (range, <1-9.5 months). Median overall survival was 11.4 months (95% CI = 5.7-15.7) and 12-month OS estimate was 45.9% (95% CI = 32.8-58.0).

Venetoclax with LDAC showed similar efficacy profiles across adverse karyotypes and varied mutational profiles. In patients with intermediate risk (n=37) and adverse risk (n=19) cytogenetics, the CR+CRi rates were 76% and 47%, respectively, with median OS of 15.7 and 5.7 months, respectively. In 27 patients with secondary AML, the CR+CRi rate was 52%. In patients with *FLT3-ITD* (n=9), *FLT3-TKD* (n=5) or *IDH1/2* (n=14) mutations, the CR+CRi rates were 67%, 40% and 71%, respectively.

AEs of any grade occurring in ≥40% of patients included: nausea, hypokalemia, diarrhea, fatigue, and decreased appetite. Grade 3/4 AEs (≥10%) included febrile neutropenia, hypokalemia, pneumonia, AML progression, hypophosphatemia, hypertension, and sepsis. Grade 3 TLS was reported in 1 patient. Deaths were reported in 3% (n=2) of patients ≤30 days after the start of treatment and 13% (n=8) of patients ≤60 days after the start of treatment.

A randomized, double-blind, placebo-controlled, Phase 3 study is evaluating the efficacy and safety of venetoclax co-administered with LDAC versus placebo with LDAC in newly diagnosed AML who are ≥18 years and are ineligible for intensive chemotherapy[6]. Based on the efficacy and safety data from the Phase 1/2 study above, patients will receive venetoclax 600 mg or placebo with LDAC.

Respectfully submitted,

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Cited References:

1. DiNardo CD, Pratz KW, Letai A, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, Phase 1b study. *Lancet Oncol.* 2018;19(2):216-228.
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3. Strickland SA, Chyla B, Popovic R, et al. Cytogenetic and molecular drivers of outcome with venetoclax-based combination therapies in treatment-naïve elderly patients with AML. Presented at the European Hematology Association (EHA) 23rd Annual Meeting; June 14–17, 2018; Stockholm, Sweden. Poster PS982.
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5. Wei AH, Strickland SA, Roboz GJ, et al. Phase 1/2 study of venetoclax with low-dose cytarabine in treatment-naive, elderly patients with acute myeloid leukemia unfit for intensive chemotherapy: 1 year outcomes. Presented at: 59th American Society of Hematology Annual Meeting and Exposition; December 9-12, 2017; Atlanta, GA. Oral Presentation 890.
6. ClinicalTrials.gov: A randomized, double-blind, placebo controlled Phase 3 study of venetoclax co administered with low dose cytarabine versus low dose cytarabine in treatment naïve patients with acute myeloid leukemia who are ineligible for intensive chemotherapy. NLM Identifier: NCT03069352. ClinicalTrials.gov Web site. https://clinicaltrials.gov/ct2/show/NCT03069352. Last updated June 14, 2018. Accessed June 27, 2018.