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NCCN Guidelines® Panel: Non-Hodgkin's Lymphoma

On behalf of AbbVie and Genentech, I respectfully request the NCCN Non-Hodgkin's Lymphoma (NHL) Guideline Panel to consider the enclosed data for Venclexta™ (venetoclax) for use as monotherapy in the treatment of patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) with 17p deletion [del(17p)] as detected by an FDA approved test.

Specific Changes: Consider the available data on the use of Venclexta for the treatment of R/R CLL patients with del(17p) for your updating purposes.

Also provided for your consideration is clinical data studying the use of Venclexta in the broader R/R CLL patient population, including patients harboring del(17p).

FDA Clearance: On April 11, 2016, the FDA approved Venclexta (venetoclax) for the treatment of patients with CLL with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication is contingent upon verification and description of clinical benefit in a confirmatory trial. This follows the provision by the FDA of a "Breakthrough Therapy Designation" received on May 6, 2015 to Venclexta for the treatment of R/R CLL patients with del(17p). Please refer to the enclosed full prescribing information for the FDA approved indication, including safety information.

Rationale: Venclexta has demonstrated antitumor activity resulting in response as measured by overall response rate (ORR), complete response (CR), progression-free survival (PFS), overall survival (OS), and duration of response (DOR) in R/R CLL patients with del (17p).¹

Supporting Literature: Stilgenbauer et al. reported the results of a Phase 2 single-arm, multicenter study focused on a population of 107 patients with R/R CLL with del(17p).¹ One enrolled patient did not harbor the 17p deletion. The primary endpoint was ORR. Among the secondary endpoints were DOR, PFS, OS, and safety. Minimal residual disease (MRD) was an exploratory endpoint. ORR was achieved in 79.4% of patients with a 7.5% CR/CRi rate, as assessed by an independent review committee (IRC). The estimated PFS and OS at 12 months were 72% and 86.7%, respectively. The estimated DOR at 12 months was 84.7% for all responders. Median time to first response was 0.8 months (0.1-8.1). The exploratory MRD endpoint analysis showed that of 45 patients tested, 18 (16.8% of full population) achieved MRD

negativity in peripheral blood. Adverse events of any grade occurring in $\geq 20\%$ of patients included: neutropenia, diarrhea, nausea, anemia, fatigue, and pyrexia. Grade 3 or 4 adverse events occurring in $\geq 10\%$ of patients included: neutropenia, anemia, and thrombocytopenia. Laboratory tumor lysis syndrome (TLS) was observed in 5 patients during the ramp-up period; none had clinical consequences.

Roberts et al, as published in the New England Journal of Medicine, reported on a Phase I dose escalation study with a total of 116 heavily-pretreated (median 3 prior therapies) patients with CLL or small lymphocytic lymphoma (SLL).² The primary endpoints included assessment of safety. Secondary endpoints included evaluation of response rates and other measures of efficacy such as PFS and OS. The median duration of follow-up for all 116 patients was 17 months. In the dose-escalation and expansion cohort the pooled ORR was 79% and the CR rate was 20%. Five percent of all study patients had no MRD as measured in bone marrow. In a subpopulation of 31 patients with del(17p), the ORR was 71% and the CR rate was 16%. The median PFS for patients with del(17p) across all doses was 16 months. In the dose escalation cohort, the median PFS was 25 months with a median follow-up of 21 months. In the expansion cohort, the PFS at 15 months was estimated to be 66% with a median follow-up of 17 months. The 2-year overall survival estimate for all patients was 84%. Adverse events of any grade occurring in $\geq 40\%$ of patients included: diarrhea, upper respiratory tract infection, nausea, neutropenia, and fatigue. Grade 3 or 4 adverse events occurring in $\geq 5\%$ of patients included: neutropenia, anemia, thrombocytopenia, and hyperglycemia. A stepwise ramp-up dosing phase was implemented to mitigate the risk of TLS caused by the rapid reduction in tumor burden. In the dose-escalation cohort, 10 of 56 patients (18%) experienced TLS prior to implementation. Three patients had clinical TLS while laboratory TLS occurred in 7 patients (8 episodes). In the expansion cohort, 1 patient had laboratory evidence of TLS and no clinical TLS was observed following implementation of the mitigation strategy.

The following key study publications are submitted with the full FDA prescribing information.

1. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax (ABT-199/GDC-0199) monotherapy induces deep remissions, including complete remission and undetectable MRD, in ultra-high risk relapsed/refractory chronic lymphocytic leukemia with 17p deletion: results of the pivotal international phase 2 study. Presented at: American Society of Hematology Annual Meeting and Exposition; December 5-8, 2015; Orlando, FL. Oral Presentation LBA-6.
2. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016; 374(4):311-322.

Respectfully submitted,



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