

Submitted by:

Catherine Miller, Pharm.D.

Global Medical Information, Medical Affairs

AbbVie Inc.

ABV1-2NW10201

1 North Waukegan Rd

North Chicago, IL 60064

Phone: 847-935-1483

Email: catherine.miller@abbvie.com

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NCCN Guidelines® Panel: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

On behalf of AbbVie and Genentech, I respectfully submit the enclosed to the NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Guideline:

- Venclexxa® (venetoclax): Relapsed/refractory (R/R) Chronic Lymphocytic Leukemia (CLL)
 - Seymour JF, Klipps TJ, Eichhorst BF, et al. Venetoclax plus rituximab is superior to bendamustine plus rituximab in patients with relapsed/refractory chronic lymphocytic leukemia—results from pre-planned interim analysis of the randomized phase 3 Murano study. American Society of Hematology Website.
<https://ash.confex.com/ash/2017/webprogram/Paper109076.html>. Accessed November 27, 2017
 - Seymour JF, Kipps TJ, Eichhorst BF, et al. Venetoclax plus rituximab is superior to bendamustine plus rituximab in patients with relapsed/refractory chronic lymphocytic leukemia – results from pre-planned interim analysis of the randomized phase 3 Murano study. Presented at: American Society of Hematology 59th Annual Meeting and Exposition; December 9-12, 2017; Atlanta, GA. LBA-2.

Specific Changes:

- Please consider the above publication and oral presentation for your updating purposes. Additional trials have been conducted to evaluate the combination of Venclexxa® plus Rituxan® in R/R CLL.

FDA Clearance:

- Venclexxa® in combination with rituximab is not approved by the US Food and Drug Administration (FDA) for the treatment of R/R CLL.¹
 - Please refer to the product prescribing information for the full FDA-approved indications and safety information.
 - Full Venclexxa® prescribing information available at:
<http://www.rxabbvie.com/pdf/venclexxa.pdf>
- Rituxan® in combination with Venclexxa® is not approved by the US FDA for the treatment of R/R CLL.²
 - Please refer to the product prescribing information for the full FDA-approved indications and safety information.
 - Full Rituxan® prescribing information available at:
https://www.gene.com/download/pdf/rituxan_prescribing.pdf

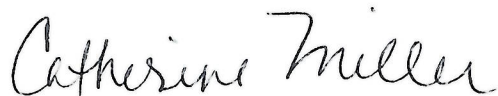
Rationale: Venclexta® is a novel, Bcl-2 inhibitor that works synergistically with Rituxan® to augment responses in CLL with comparable adverse events (AEs) to Venclexta® monotherapy.³

Seymour et al., recently presented on the first Phase 3 open-label, randomized study of Venclexta® in combination with Rituxan® at the 2017 American Society of Hematology Annual Meeting.^{4,5} Patients were randomized 1:1 to Venclexta® plus Rituxan® [(VR), n=194] or bendamustine plus Rituxan® [(BR) n=195]. Patients in the VR arm followed a 4 or 5 week V dose ramp up schedule to mitigate the risk of tumor lysis syndrome (TLS). Following ramp-up, R was dosed for six 28-day cycles combined with daily V. Patients continued V for a maximum of 2 years or until disease progression. In the BR arm, patients received B with R for six 28-day cycles. The primary endpoint was investigator (INV)-assessed progression free survival (PFS). Interim analysis occurred for approximately 140 INV-assessed PFS events. As of the cut-off date of May 8, 2017, the median follow-up was 23.8 months (range 0-37.4 months). Venclexta® plus Rituxan® demonstrated superiority in INV-assessed PFS, overall response rate, and complete remission (CR) or CR with incomplete marrow recovery. Grade 3/4 AEs (≥5%) included cytopenias, febrile neutropenia, pneumonia, and infusion-related reaction. There were 6 and 2 events of Grade ≥3 TLS in VR and BR, respectively; one event of clinical TLS occurred in each arm. Deaths were reported in 5.2% vs 5.9% of patients with VR and BR, respectively.

Cited Reference:

1. Venclexta® [package insert]. AbbVie, Inc. 2016.
2. Rituxan® [package insert]. Genentech, Inc. 2016.
3. Seymour JF, Ma S, Brander DM, et al. Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b study. *Lancet Oncol.* 2017;18(2):230-240.
4. Seymour JF, Klipps TJ, Eichhorst BF, et al. Venetoclax plus rituximab is superior to bendamustine plus rituximab in patients with relapsed/refractory chronic lymphocytic leukemia—results from pre-planned interim analysis of the randomized phase 3 Murano study. American Society of Hematology Website. <https://ash.confex.com/ash/2017/webprogram/Paper109076.html>. Accessed November 27, 2017.
5. Seymour JF, Kipps TJ, Eichhorst BF, et al. Venetoclax plus rituximab is superior to bendamustine plus rituximab in patients with relapsed/refractory chronic lymphocytic leukemia – results from pre-planned interim analysis of the randomized phase 3 Murano study. Presented at: American Society of Hematology 59th Annual Meeting and Exposition; December 9-12, 2017; Atlanta, GA. LBA-2.

Respectfully submitted,



Catherine Miller, Pharm.D.

Senior Manager, Global Medical Information, AbbVie Inc.