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NCCN Guidelines® Panel: Non-Hodgkin's Lymphomas

Dear NCCN,

Pharmacyclics LLC and Janssen Biotech, Inc. co-develop and co-commercialize IMBRUVICA® (ibrutinib) capsules. On behalf of Pharmacyclics LLC and Janssen Biotech, Inc., I respectfully request the NCCN Guidelines® - Non-Hodgkin's Lymphomas Panel review the enclosed, updated information for inclusion of the following IMBRUVICA (ibrutinib) combination therapies for the treatment of patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL).

Specific Change:
Recommend IMBRUVICA (ibrutinib) for the treatment of patients with R/R CLL for each of the following treatment options:

- Single-agent therapy: remain listed as Category 1
- Combination therapy with bendamustine and rituximab (BR): addition to currently listed options
- Combination therapy with ofatumumab: addition to currently listed options

FDA Clearance:
The U.S. Food and Drug Administration (FDA) approved IMBRUVICA (ibrutinib) for the treatment of patients with CLL who have received at least one prior therapy, CLL with 17p deletion, mantle cell lymphoma who have received at least one prior therapy (accelerated approval was granted for this indication based on overall response rate; continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials), and Waldenström's macroglobulinemia.[1]

Ibrutinib is not currently approved by the FDA for R/R CLL in combination with BR or in combination with ofatumumab.

Rationale:
Recent, full publications are now available to support the use of ibrutinib in combination with other therapies for the treatment of patients with R/R CLL including a manuscript in *Lancet Oncology*[2], which, in addition to presentations at major congresses[3-9], reports results from the randomized Phase 3 HELIOS trial of ibrutinib + BR vs. placebo + BR (N=578 R/R CLL/small lymphocytic lymphoma [SLL] patients; CLL3001, NCT01611090), and a manuscript in *Blood*, which reports results from a Phase 1b/2 open-label study of ibrutinib + ofatumumab in patients with R/R CLL/SLL, prolymphocytic leukemia, or Richter's transformation (N=71; PCYC-1109, NCT01217749).[10]

A supplemental New Drug Application (sNDA) was submitted to the FDA on November 13, 2015 for labeling considerations based on the Phase 3 HELIOS (CLL3001) data.[11]

The following references are submitted with the full Prescribing Information[1] in support of the proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

1. IMBRUVICA® (ibrutinib) [package insert]. Sunnyvale, CA: Pharmacyclics LLC; 2015.
2. Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma: a randomised, double-blind, phase 3 study [published online Dec 4 2015]. *Lancet Oncol.* 2015. http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(15)00465-9.pdf.
3. Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab (BR) in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): First results from a randomized, double-blind, placebo-controlled, phase III study [oral presentation]. American Society of Clinical Oncology Annual Meeting; May 29-June 2, 2015; Chicago, IL. Abstract LBA7005.
4. Chanan-Khan A, Cramer P, Demirkan F, et al. Insights into the management of adverse events in patients with previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma: Experience from the phase 3 HELIOS study of ibrutinib combined with bendamustine/rituximab [oral presentation]. American Society of Hematology Meeting on Hematologic Malignancies; Sep 17-19, 2015; Chicago, IL. Abstract 6.
5. Chanan-Khan A, Cramer P, Fraser G, et al. Impact of high risk prognostic parameters and addition of ibrutinib to bendamustine/rituximab (BR) on outcomes for patients with relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) from the phase 3 double-blind HELIOS trial [poster presentation]. 57th Annual Meeting and Exposition of the American Society of Hematology; Dec 5-8, 2015; Orlando, FL. Abstract 1732.
6. Cramer P, Chanan-Khan A, Fraser G, et al. Improvement of quality of response with ibrutinib plus bendamustine/rituximab vs placebo plus bendamustine/rituximab for previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) [poster presentation]. 57th Annual Meeting and Exposition of the American Society of Hematology; Dec 5-8, 2015; Orlando, FL. Abstract 2938.
7. Traina S, Fraser G, Cramer P, et al. Ibrutinib plus bendamustine/rituximab (BR) is associated with greater reductions in fatigue than placebo plus BR among patients with relapsed/refractory chronic lymphocytic leukemia and fatigue [abstract]. *Blood.* 2015:Abstract 267. https://ash.confex.com/ash/2015/webprogram/Paper80274.html.
8. Cramer P, Chanan-Khan A, Fraser G, et al. Ibrutinib combined with bendamustine/rituximab (BR) in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): safety analysis in the HELIOS trial [oral presentation]. 16th International Workshop on Chronic Lymphocytic Leukaemia; Sep 7-9, 2015; Sydney, Australia.
9. Fraser G, Chanan-Khan A, Cramer P, et al. Ibrutinib combined with bendamustine/rituximab in previously treated CLL/SLL: subgroup efficacy analyses from the HELIOS trial [oral presentation]. 16th International Workshop on Chronic Lymphocytic Leukaemia; Sep 7-9, 2015; Sydney, Australia.
10. Jaglowski SM, Jones JA, Nagar V, et al. Safety and activity of BTK inhibitor ibrutinib combined with ofatumumab in chronic lymphocytic leukemia: a phase 1b/2 study. *Blood.* 2015;126(7):842-850. http://www.bloodjournal.org/content/126/7/842.
11. AbbVie submits IMBRUVICA® (ibrutinib) phase III combination data to U.S. FDA [press release]. Chicago, IL: Abbvie Inc; Nov 13,. 2015; http://www.prnewswire.com/news-releases/abbvie-submits-imbruvica-ibrutinib-phase-iii-combination-data-to-us-fda-300178296.html. Accessed November 13, 2015.

Sincerely,

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