February 27, 2017

Name: Alex Young, PharmD
Company/Organization: Pharmacyclics LLC, an AbbVie Company
Address: 995 East Arques Avenue, Sunnyvale, CA 94085
Phone: 408.215.3412
E-mail: alyoung@pcyc.com
Date of request: February 27, 2017
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 to review the enclosed information of IMBRUVICA (ibrutinib) for the treatment of chronic lymphocytic leukemia (CLL) and/or small lymphocytic lymphoma (SLL).

Specific Change: Consider the available data on outcomes post-discontinuation of IMBRUVICA in patients with CLL and/or SLL for your updating purposes.

FDA Clearance:
IMBRUVICA® is a kinase inhibitor indicated for the treatment of patients with:

- Mantle cell lymphoma (MCL) 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 and description of clinical benefit in a confirmatory trial.
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Rationale: Several articles have reported on patient characteristics and clinical outcomes post-ibrutinib discontinuation in patients with CLL/SLL, including median survival and/or time to discontinuation stratified by factors for stopping ibrutinib therapy.

- Maddocks et al (2015)[2] published a retrospective analysis of time to discontinuation, reason for discontinuation, and survival following discontinuation of ibrutinib-based therapy in patients with CLL/SLL (N=308; n=76 discontinued) enrolled in 4 sequential trials at the Ohio State University Comprehensive Cancer Center (PCYC-1102 [NCT01105247], PCYC-1109 [NCT01217749], OSU-11133 [NCT01589302], RESONATE™ [PCYC-1112, NCT01578707]).
- Jain et al (2015)[3] published a retrospective analysis of patient characteristics and causes and outcomes of discontinuation of ibrutinib with or without rituximab in patients with CLL/SLL (N=127; n=33 discontinued) enrolled in 4 clinical trials at the MD Anderson Cancer Center (PCYC-1102 [NCT01105247], NCT01520519, RESONATE™ [PCYC-1112, NCT01578707], NCT01752426).
- Mato et al (2016)[4] published a multicenter retrospective cohort analysis of patients with CLL on or off clinical trials who discontinued ibrutinib (n=143) or idelalisib-based (n=35) therapy for any reason.

- Mato et al (2016)[5] presented a multicenter retrospective analysis of ibrutinib-treated patients with CLL (N=621; 40% discontinued) and outcomes by reason for discontinuation.
- Jain et al (2016)[6] presented long-term outcomes for patients with CLL/SLL (N=320; n=90 discontinued) on clinical studies discontinuing ibrutinib-based regimens from the MD Anderson Cancer Center.
- O'Brien et al (2016)[7] reported outcomes with ibrutinib treatment based on prior lines of therapy and following ibrutinib discontinuation in patients with CLL (N=271) from the RESONATE™ (NCT01578707) and RESONATE™-2 (NCT01722487) studies.
- Parikh et al (2015)[8] conducted a retrospective study of baseline characteristics, time, reasons for discontinuation, and survival following discontinuation in patients with CLL (N=135; n=25 discontinued) treated with commercial ibrutinib.
- Sandoval-Sus et al (2015)[9] reported patient characteristics, reasons for discontinuation, and outcomes following discontinuation of ibrutinib in CLL (N=54; n=22 discontinued) in the Moffitt Cancer Center.

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 the NCCN panel members who are also co-authors or co-contributors of these publications.

1. IMBRUVICA® (ibrutinib) [prescribing information]. Sunnyvale, CA: Pharmacyclics LLC; 2017.
2. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncol.* 2015;1(1):80-87. http://jamanetwork.com/journals/jamaoncology/fullarticle/2120915
3. Jain P, Keating M, Wierda W, et al. Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib. *Blood.* 2015;125(13):2062-2067. http://www.bloodjournal.org/content/125/13/2062
4. Mato AR, Nabhan C, Barr PM, et al. Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience. *Blood.* 2016;128(18):2199-2205. http://www.bloodjournal.org/content/bloodjournal/early/2016/09/07/blood-2016-05-716977.full.pdf
5. Mato AR, Lamanna N, Ujjani CS, et al. Toxicities and outcomes of ibrutinib-treated patients in the United States: large retrospective analysis of 621 real world patients [abstract]. *Blood.* 2016;128(22):Abstract 3222. https://ash.confex.com/ash/2016/webprogram/Paper94489.html
6. Jain P, Thompson PA, Keating M, et al. Causes of discontinuation and long-term outcomes of patients with CLL after discontinuing ibrutinib [abstract]. *Blood.* 2016;128(22):Abstract 4390. https://ash.confex.com/ash/2016/webprogram/Paper95542.html
7. O'Brien SM, Byrd JC, Hillmen P, et al. Outcomes with ibrutinib by line of therapy in patients with CLL: analyses from phase 3 data [abstract]. *J Clin Oncol.* 2016;34:Abstract 7520. http://abstracts.asco.org/176/AbstView_176_164543.html
8. Parikh SA, Chaffee KR, Call TG, et al. Ibrutinib therapy for chronic lymphocytic leukemia (CLL): an analysis of a large cohort of patients treated in routine clinical practice [abstract]. *Blood.* 2015;126(23):Abstract 2935. http://www.bloodjournal.org/content/126/23/2935
9. Sandoval-Sus JD, Chavez JC, Dalia S, et al. Outcomes of patients with relapsed/refractory chronic lymphocytic leukemia after ibrutinib discontinuation outside clinical trials: a single institution experience [abstract]. *Blood.* 2015;126(23):Abstract 2945. http://www.bloodjournal.org/content/126/23/2945

Sincerely,

Alex Young, PharmD
Senior Specialist, Scientific Communications
Pharmacyclics LLC, an AbbVie Company