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NCCN Guidelines® Panel: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Dear NCCN:

Pharmacyclics LLC and Janssen Biotech, Inc. co-develop and co-commercialize IMBRUVICA® (ibrutinib). On behalf of Pharmacyclics LLC and Janssen Biotech, Inc., I respectfully request the NCCN Guidelines® - CLL/SLL Panel to review the enclosed information of IMBRUVICA (ibrutinib) for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma.

Specific Change: Consider the available data on IMBRUVICA in patients with CLL/SLL for your updating purposes.

FDA Clearance:
IMBRUVICA® is a kinase inhibitor indicated for the treatment of adult patients with:[1]

- 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.
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

Rationale: **Burger et al (2018)[2,3]** recently presented updated results from the randomized, Phase 3 RESONATE™-2 study of single-agent ibrutinib (ibr) vs chlorambucil (clb) in patients ≥65 years with treatment naïve (TN) CLL/SLL (N=269) (PCYC-1115, NCT01722487). With a median follow-up of 48 months, significantly longer progression-free survival (PFS) was observed with ibr vs. clb, with an 86% reduction in risk of progressive disease or death (HR 0.137; 95% CI 0.090-0.210).[3] Improved PFS with ibr vs clb was also observed in high-risk subgroups such as del11q (HR 0.034; 95% CI: 0.011-0.110) and unmutated *IGHV* (HR 0.088; 95% CI: 0.046-0.169);[3] however, the study was not designed to test treatment effect in subpopulations. Overall response rate was 91% vs 37% in the ibr vs clb arm.[2] Complete response rate with ibr was 16.2% (sponsor-confirmed),[3] an increase from 4% (IRC-confirmed) at the primary analysis (**Burger et al [2015]**[4] at a median follow-up of 18.4 mo).

The most common grade ≥3 adverse events (≥5%) over the 4-year follow-up period for patients treated with ibrutinib included: neutropenia (13%), pneumonia (12%), anemia (7%), hypertension (7%), and hyponatremia (5%).[3] Atrial fibrillation occurred in 13% of ibrutinib-treated patients (Gr ≥3: 4%) and major hemorrhage occurred in 10%.[3] Discontinuation of ibrutinib due to adverse events occurred in 19% of patients, and 73% of patients received ibrutinib treatment for 3 years or longer.[3]

For further information, results from an earlier follow-up of RESONATE™-2, after median treatment duration of 28.5 mo, were originally presented at the 2016 Annual Meeting of the American Society of Hemtology (ASH)[5] and have recently been published by **Barr et al (2018)**.[6]

The following references are submitted with the full prescribing information[1] as support. 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; 2018.
2. Burger J, Barr P, Robak T, et al. IBRUTINIB FOR FIRST-LINE TREATMENT OF OLDER PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL): A 4-YEAR EXPERIENCE FROM THE RESONATE-2 STUDY [abstract]. *Haematologica.* 2018:Abstract PF343. https://learningcenter.ehaweb.org/eha/2018/stockholm/214817/
3. Burger J, Barr PM, Robak T, et al. Ibrutinib for first-line treatment of older patients with chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL): A 4-year experience from the RESONATE-2 study [poster presentation]. 23rd Congress of the European Hematology Association; 2018; Stockholm, Sweden. Abstract PF343.
4. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *The New England Journal of Medicine.* 2015;373(25):2425-2437. http://www.nejm.org/doi/full/10.1056/NEJMoa1509388
5. Barr P, Robak T, Owen C, et al. Updated efficacy and safety from the phase 3 RESONATE-2 study: ibrutinib as first-line treatment option in patients 65 years and older with chronic lymphocytic leukemia/small lymphocytic lymphoma [abstract]. *Blood.* 2016;128(22):Abstract 234. https://ash.confex.com/ash/2016/webprogram/Paper89615.html
6. Barr PM, Robak T, Owen C, et al. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2. *Haematologica.* 2018.


Sincerely,


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