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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 on IMBRUVICA (ibrutinib) for the treatment of CLL/SLL.

Specific Changes: Please find below updates for your consideration.

<table>
<tr><th colspan="2">Indication</th><th>Specific Request</th></tr>
<tr><td>CLL/SLL without del(17p)/TP53 mutation<br>First-Line Therapy</td><td>Frail patient with significant comorbidity<br>OR<br>Patients age ≥65 y and younger patients with significant comorbidities</td><td rowspan="3">• Ibrutinib: Consider the data summarized below for updating purposes to support Ibrutinib's current placement as a Category 1, Preferred regimen</td></tr>
<tr><td colspan="2">CLL/SLL without del(17p)/TP53 mutation<br>R/R Therapy</td></tr>
<tr><td colspan="2">CLL/SLL with del(17p)/TP53 mutation<br>R/R Therapy</td></tr>
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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:

**In CLL/SLL without del(17p)/TP53 mutation, First-Line Therapy, for "Frail patient with significant comorbidity" or "Age ≥65 y and younger patients with significant comorbidities":**

- Consider the data summarized below for updating purposes to support **Ibrutinib's** current placement as a **Category 1, Preferred regimen**

*RESONATE-2*[2-4]

- Updated results from the Phase 3 RESONATE™-2 study (PCYC-1115/1116; NCT01722487, NCT01724346) of first-line single-agent ibrutinib (ibr) vs chlorambucil (clb) in patients ≥65 years with treatment naïve (TN) CLL/SLL without del(17p) (N=269) were recently presented by **Tedeschi et al.** A summary of results as described by the authors is provided below.
  - With a median follow-up of 5 years (range, 0.1-66 mo), ibr continues to sustain (investigator-assessed) progression-free survival (PFS) benefit vs clb, with an 85% reduction in risk of progressive disease or death (HR 0.15; 95% CI, 0.10-0.22). Median PFS has not been reached in the ibr arm; and the estimated 5-yr PFS rates are 70% for ibr vs 12% for clb. Only 8 patients (6%) progressed while receiving ibr. Improved PFS with ibr vs clb continues to be observed in patients with high-risk genomic features, such as unmutated *IGHV* (HR 0.11; 95% CI: 0.06-0.19) and del11q (HR 0.03; 95% CI: 0.01-0.11); however, the study was not designed to test treatment effect in subpopulations. In addition, ibr continues to demonstrate an overall survival (OS) benefit vs clb (HR 0.450; 95% CI, 0.266-0.761); estimated 5-yr OS rates are 83% for ibr vs 68% for clb, even with 57% of patients crossing over from clb to ibr after progression.
  - The most common Grade ≥3 adverse events (≥5%) over the 5-year follow-up period for patients treated with ibrutinib include: neutropenia (13%), pneumonia (12%), hypertension (8%), anemia (7%), hyponatremia (6%), atrial fibrillation (5%), and cataract (5%). Discontinuations of ibrutinib due to adverse events decreased over time, and 58% of patients remain on therapy. Active dose management (dose holds and reductions) to address adverse events enables ~90% patients to continue on ibrutinib.
  - This analysis provides the longest follow-up to date from a Phase 3 study of first-line BTK-directed therapy for CLL. With up to 5.5 years of follow-up, the PFS was 70% at 5 years, nearly six out of ten patients remain on continuous single-agent ibr treatment, and no new safety signals have emerged.

**In CLL/SLL without del(17p)/TP53 mutation, Relapsed/Refractory Therapy AND**
**In CLL/SLL with del(17p)/TP53 mutation, Relapsed/Refractory Therapy:**

- Consider the data summarized below for updating purposes to support **Ibrutinib's** current placement as a **Category 1, Preferred regimen**

*RESONATE*[5,6]

- The final analysis of the Phase 3 RESONATE™ study (PCYC-1112; NCT01578707) of single-agent ibrutinib (ibr) vs ofatumumab (ofa) in patients with relapsed/refractory (R/R) CLL/SLL (N=391) was recently presented by **Barr et al.** A summary of results as described by the authors is provided below.
  - With a median follow-up of 65.3 mo (range, 0.3-71.6 mo) on ibr, ibr showed sustained benefit in (investigator-assessed) progression-free survival (PFS) benefit vs ofa, with a median PFS of 44.1 mo vs. 8.1 mo (HR 0.15; 95% CI, 0.11-0.20). Estimated 5-yr PFS rates were 40% for ibr vs 3% for ofa. In patients with high-risk genomic features (del17p, del11q, TP53 mutation, and/or unmutated IGHV), which comprised 86% of the ibr arm and 79% of the ofa arm, median PFS was 44.1 on ibr vs 8.0 mo on ofa (HR 0.11; 95% CI, 0.08-0.15). Median overall survival (OS) was 67.7 mo in the ibr arm vs 65.1 mo in the ofa arm, without censoring or adjustment for crossover (HR 0.810; 95% CI, 0.602-1.091). Sensitivity analysis adjusting for crossover showed OS benefit with ibr compared with ofa (HR 0.24; 95% CI, 0.105-0.550); 68% of patients initially assigned to the ofa arm crossed over to receive ibr.
  - Median duration of treatment with ibr was 41 mo (range, 0.2-71), and 41% of patients received ibr for >4 yrs. With regards to specific adverse events (AEs), all-grade hypertension occurred in 21% (Gr ≥3:

9%), all-grade atrial fibrillation occurred in 12% (Gr ≥3: 6%), and major hemorrhage occurred in 10% of patients. Discontinuation of ibrutinib due to AEs occurred in 16% of patients.

- With up to 6 years of follow-up, this analysis provides the longest follow-up to date from a Phase 3 study of a BTK inhibitor in patients with R/R CLL, characterizing the long-term efficacy and safety profile of continuous ibr treatment.

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; 2019. https://www.imbruvica.com/docs/librariesprovider7/default-document-library/prescribing-information.pdf.
2. Tedeschi A, Burger J, Barr PM, et al. FIVE-YEAR FOLLOW-UP OF PATIENTS RECEIVING IBRUTINIB FOR FIRST-LINE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA [abstract]. *Haematologica.* 2019:Abstract S107. https://learningcenter.ehaweb.org/eha/2019/24th/267308/alessandra.tedeschi.five-year.follow-up.of.patients.receiving.ibrutinib.for.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dibrutinib
3. Tedeschi A, Burger J, Barr PM, et al. Five-Year Follow-Up of Patients Receiving Ibrutinib for First-Line Treatment of Chronic Lymphocytic Leukemia [oral presentation]. 24th Congress of the European Hematology Association; June 13 - 16, 2019; Amsterdam, Netherlands. Abstract S107.
4. Tedeschi A, Burger J, Barr PM, et al. FIVE-YEAR FOLLOW-UP OF FIRST-LINE IBRUTINIB FOR TREATMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA//SMALL LYMPHOCYTIC LYMPHOMA [abstract]. *Hematol Oncol.* 2019:Abstract 061. https://onlinelibrary.wiley.com/doi/10.1002/hon.67_2629
5. Barr PM, Munir T, Brown JR, et al. Final Analysis from RESONATE: 6-year Follow-up in Patients (Pts) With Previously Treated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (CLL/SLL) on Ibrutinib [abstract]. *Journal of Clinical Oncology.* 2019;37(suppl):Abstract 7510. https://meetinglibrary.asco.org/record/174673/abstract
6. Barr PM, Munir T, Brown JR, et al. 6-year Follow-up from RESONATE in Patients With Previously Treated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma on Ibrutinib [poster presentation]. 55th Annual Meeting of the American Society of Clinical Oncology; May 31 - June 4, 2019; Chicago, IL. Abstract 7510.


Sincerely,


Judy Wu, PharmD
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Pharmacyclics LLC, an AbbVie Company