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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 regarding IMBRUVICA (ibrutinib) for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma.

Specific Changes: Please find below proposed changes for your consideration.

Indication		**Specific Change**
CLL/SLL without del(17p)/TP53 mutation First-Line Therapy	Across patient age and co-morbidity status	• Recommend inclusion of IGHV status in clinical decision tree for therapy determination. (Affected pages may include CSLL-3, 4, 5, and updates to the relevant suggested treatment regimens on CSLL-D)
	Frail patient with significant comorbidity *and* Age ≥65 y and younger patients with significant comorbidities	• **Ibrutinib:** Retain as Category 1, preferred regimen, for patients with unmutated and mutated IGHV • **Ibrutinib + CD20 monoclonal antibody:** Recommend as Category 1, preferred regimen, for patients with unmutated and mutated IGHV
	Age <65 y without significant comorbidities	• **Ibrutinib + rituximab:** Recommend as Category 1, preferred regimen, for patients with unmutated and mutated IGHV

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

The use of ibrutinib in combination with a CD20 monoclonal antibody (e.g. rituximab, obinutuzumab) for the treatment of CLL/SLL is not currently approved by the FDA.

Rationale:

In CLL/SLL without del(17p)/TP53 mutation, First-Line Therapy, across patient age and co-morbidity status:

- Recommend inclusion of IGHV status in clinical decision tree for therapy determination (Affected pages may include CSLL-3, 4, 5, and updates to the relevant suggested treatment regimens on CSLL-D.)

Explanation:

- In the rapidly evolving CLL treatment landscape, the role of IGHV mutational status in treatment selection has gained increasing prominence.
- The current NCCN Guidelines® for CLL/SLL (v.2.2019)[2] as well as the recently updated 2018 iwCLL guidelines[3] recommend molecular analysis to detect IGHV mutation status at baseline.
- In addition, several recently published treatment algorithms for the management of patients with CLL[4-8] recommend consideration of IGHV status when selecting treatment options, especially since unmutated IGHV disease has been associated with inferior outcomes compared to mutated IGHV disease with a certain regimen. (In patients with mutated IGHV disease, treatment with this specific regimen may still be considered a reasonable option.)
- Therefore, incorporating IGHV status into the CLL/SLL clinical decision tree highlights the importance of IGHV mutation testing and the need to account for relevant patient characteristics and risk factors when selecting the most appropriate treatment option for patients with CLL/SLL.

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":

- **Retain Ibrutinib as Category 1, preferred regimen, for IGHV mutated and unmutated patients**
- **Recommend Ibrutinib + CD20 monoclonal antibody as Category 1, preferred regimen, for IGHV mutated and unmutated patients**

ALLIANCE[9]

- The primary results from the Phase 3 ALLIANCE (A041202; NCT01886872) study were recently published and presented as a plenary oral at the 2018 American Society of Hematology (ASH) Annual Meeting by **Woyach et al.** In this Phase 3 trial, patients 65 years of age or older with untreated CLL were randomized 1:1:1 to receive bendamustine + rituximab (BR), ibrutinib (I), or ibrutinib + rituximab (IR).
- With a median follow-up of 38 months (among 481 patients still alive), both I and IR reduced the risk of progression or death vs BR (I vs BR: HR 0.39; 95% CI, 0.26-0.58, p<0.001 and IR vs BR: HR 0.38; 95% CI, 0.25-0.59, p<0.001). However, there was no significant difference between the I and IR groups with respect to PFS (IR vs I: HR 1.00; 95% CI, 0.62-1.62, p=0.49). The estimated 2-year PFS rates were 74% with BR, 87% with I, and 88% with IR. In the discussion section of the ALLIANCE manuscript, the authors acknowledge that the study was not powered to detect differences among subgroups; however, they describe that, in subgroup analyses, treatment with the I and IR regimens appeared to result in longer PFS than treatment with BR in all cytogenetic factor-related subgroups, as well as among patients with IgVH-mutated and IgVH-unmutated disease. There was no significant difference among the three treatment groups with regards to overall survival (P≥0.65 for all pairwise comparisons)
- As for safety, this trial focused on Grade ≥3 adverse events of special interest that occurred during treatment and follow-up, excluding events post-crossover. Grade ≥3 hematologic adverse events were

higher with BR (61%) compared to I (41%) and IR (39%); however, the rate of Grade ≥3 non-hematologic adverse events was lower with BR (63%) compared to I (74%) and IR (74%). Any grade atrial fibrillation (3% BR vs 17% I vs 14% IR) and Grade ≥3 hypertension (14% BR vs 29% I vs 34% IR) occurred less frequently in the BR arm. Deaths during the first six cycles of treatment, within 30 days after the sixth cycle (among those who completed six cycles), or within 30 days after treatment discontinuation (among those who did not complete six cycles), occurred in 1% of patients with BR, 2% with I, and 3% with IR. Deaths during treatment or within 30 days after treatment discontinuation occurred in 1% with BR, 7% with I, and 7% with IR.

ILLUMINATE[10]

- The primary results from the Phase 3 iLLUMINATE (PCYC-1130; NCT02264574) study were also recently published and presented at ASH 2018 by **Moreno, et al.** This Phase 3 trial enrolled patients with previously untreated CLL who were either age ≥ 65 years or age < 65 years with coexisting conditions (CIRS >6, CLcr <70 ml/min, and/or del17p/TP53). Patients were randomized 1:1 to receive ibrutinib + obinutuzumab (IG) or chlorambucil + obinutuzumab (GC). Of the 229 eligible patients, 65% had high-risk disease features, defined by the presence of del17p, TP53 mutation, del11q, or unmutated IGHV.
- With a median follow-up of 31.3 months, median PFS was significantly longer in the iG arm compared to the GC arm (Not reached vs 19.0 mo; HR 0.23, 95% CI, 0.15-0.37, p<0.0001), and a PFS benefit was also observed in the subset of patients with high-risk disease (median PFS, Not reached vs 14.7 mo; HR 0.15, 95% CI, 0.09-0.27, p<0.0001). Median overall survival was not reached in either arm (HR 0.92; 95% CI, 0.48-1.77).
- Grade 3 or 4 adverse events occurred in 68% and 70% of patients in the iG and GC arms, respectively. The most common (≥5%) Grade 3 or 4 adverse events in the iG arm were neutropenia (36%), thrombocytopenia (19%), pneumonia (7%), and atrial fibrillation (5%); in the GC arm, they were neutropenia (46%), thrombocytopenia (10%), infusion-related reactions (8%), anemia (8%), and febrile neutropenia (6%).

In CLL/SLL without del(17p)/TP53 mutation, First-Line Therapy, for "Age <65 y without significant comorbidities":

- **Recommend Ibrutinib + rituximab as Category 1, preferred regimen, for IGHV mutated and unmutated patients**

E1912[11,12]

- Results from the Phase 3 E1912 (NCT02048813) study were presented by **Shanafelt, et al.** at ASH 2018. In this Phase 3 trial, patients age ≤ 70 years with previously untreated CLL were randomized 2:1 to receive ibrutinib + rituximab (IR) or fludarabine + cyclophosphamide + rituximab (FCR). Unmutated IGHV (tested in 82% of patients) was present in 75.0% of the IR arm and 61.7% of the FCR arm.
- With a median follow-up of 33.6 months, the hazard ratio for PFS favored IR over FCR (HR 0.35; 95% CI, 0.22-0.5, p<0.00001) in the ITT population (N=529). In subgroup analyses based on IGHV status, the HR for PFS favored IR over FCR in IGHV unmutated patients (HR 0.26; 95% CI, 0.14-0.50, p<0.00001), but the HR was not statistically significant in IGHV mutated patients (HR 0.44; 95% CI 0.14-1.36, p=0.07). The HR for overall survival also favored IR over FCR (HR 0.17; 95% CI 0.05-0.54, p<0.0003) in the ITT population.
- Grade ≥3 treatment-related adverse events were observed in 58.5% and 72.1% of the patients in the IR and FCR arms, respectively, with significantly less neutropenia (22.7% vs 43.7%, p<0.0001) and infectious complications (7.1% vs 19.0%, p<0.001) in the IR arm. Grade ≥3 atrial fibrillation was higher in the IR arm (2.9% vs 0.0%, p=0.04), as was Grade ≥3 hypertension (7.4% vs 1.9%, p=0.01)

Additional reference for updating purposes:

PCYC-1102/1103 – Long-Term Follow-Up [13,14]

- Long-term follow-up data over 7 years from the Phase 1b/2 study of single-agent ibrutinib in treatment-naïve and relapsed/refractory CLL/SLL were recently presented at ASH 2018 by **Byrd, et al**.

The following references are submitted with the full prescribing information[1] in support of the proposed changes. 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.
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3. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for diagnosis, indications for treatment, response assessment and supportive management of chronic lymphocytic leukemia. *Blood.* 2018.
4. Kipps TJ, Stevenson FK, Wu CJ, et al. Chronic lymphocytic leukaemia. *Nature Reviews Disease Primers.* 2017;3:16096.
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8. Parikh SA. Chronic lymphocytic leukemia treatment algorithm 2018. *Blood Cancer J.* 2018;8(10):93.
9. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. *New England Journal of Medicine.* 2018. https://www.nejm.org/doi/full/10.1056/NEJMoa1812836
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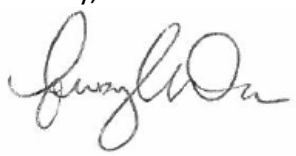
11. Shanafelt TD, Wang V, Kay NE, et al. A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL): A Trial of the ECOG-ACRIN Cancer Research Group (E1912) [abstract]. *Blood.* 2018;130:Abstract LBA-4. https://ash.confex.com/ash/2018/webprogram/Paper120779.html
12. Shanafelt T. A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL): A Trial of the ECOG-ACRIN Cancer Research Group (E1912) [oral presentation]. 60th Annual Meeting and Exposition of the American Society of Hematology; December 1-4, 2018; San Diego. Abstract LBA-4.
13. Byrd JC, Furman RR, Coutre S, et al. Up to 7 Years of Follow-up of Single-Agent Ibrutinib in the Phase 1b/2 PCYC-1102 Trial of First Line and Relapsed/Refractory Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [abstract]. *Blood.* 2018;130:Abstract 3133. https://ash.confex.com/ash/2018/webprogram/Paper110847.html
14. Byrd JC, Furman RR, Coutre S, et al. Up to 7 Years of Follow-up of Single-Agent Ibrutinib in the Phase 1b/2 PCYC-1102 Trial of First Line and Relapsed/Refractory Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [poster presentation]. 60th Annual Meeting and Exposition of the American Society of Hematology; December 1-4, 2018; San Diego. Abstract 3133.

Sincerely,



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