December 06, 2020

Name: Patrick Hardesty, PharmD, MS
Company/Organization: Pharmacyclics LLC, an AbbVie Company
Address: 995 East Arques Avenue, Sunnyvale, CA 94085
Phone: 408.215.3000
E-mail: phardesty@pcyc.com
Date of request: December 06, 2020
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 Change: Please find the below request for the committee's consideration.

Indication		Specific Request
CLL/SLL with del(17p)/TP53 mutation ***First-Line Therapy***		• Ibrutinib: Recommended guideline change to Category 1, Preferred Regimen
CLL/SLL without del(17p)/TP53 mutation ***First-Line Therapy***	Frail patient with significant comorbidity OR Patients aged ≥65 y and younger patients with significant comorbidities	• Ibrutinib: Retain as a Category 1, Preferred regimen
	Patients aged <65 y without significant comorbidities	
CLL/SLL without del(17p)/TP53 mutation ***Relapsed/Refractory***	Frail patient with significant comorbidity OR Patients aged ≥65 y and younger patients with significant comorbidities	• Bendamustine, Rituximab + Ibrutinib: Retain as Category 2B, Other recommended regimen
	Patients aged <65 y without significant comorbidities	

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 with del(17p)/TP53 mutation:

- First-Line Therapy

Long-Term Efficacy of First-line Ibrutinib Treatment for Chronic Lymphocytic Leukemia (CLL) With 4 Years of Follow-Up in Patients With TP53 Aberrations (del(17p) or TP53 Mutation): A Pooled Analysis From 4 Clinical Trials (RESONATE-2, iLLUMINATE, ECOG1912, PCYC-1122e)[2]

- Results from a pooled analysis of the phase 3 trials (RESONATE-2, iLLUMINATE, ECOG1912) and the phase 2 trial PCYC-1122e of ibrutinib-based regimens in patients with del17p/TP53 mutation were presented at ASH 2020 by **Allan et al**.
    - Eighty-nine patients with TP53 aberrations receiving first-line ibrutinib were included in the pooled analysis. All patients had either del(17p) or TP53 mutation.
    - Ibrutinib was administered as a single agent in 45 patients and in combination with an anti-CD20 in 44 patients. The median age was 65 years and 69% of patients were male.
    - With a median follow-up at 50 months, median PFS was not reached and 46% of patients with TP53 aberrations remained on ibrutinib treatment.
    - The estimated 4-year PFS rate was 79% and the 4-year OS rate was 88%.
    - The median duration of ibrutinib treatment was 46 months (range, 0.1 to 95.5 months). No new safety signals were identified during this analysis.

Outcomes of First-Line Ibrutinib in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) and High-Risk Genomic Features With Up To 6.5 Years Follow-Up: Integrated Analysis of Two Phase 3 Studies (RESONATE-2 and iLLUMINATE)[3]

- Results from an integrated analysis of the phase 3 trials, RESONATE-2 (ibrutinib versus chlorambucil) and iLLUMINATE (ibrutinib-obinutuzumab versus chlorambucil-obinutuzumab), which studied ibrutinib-based regimens in patients with high-risk genomic features, were presented at ASH 2020 by **Burger et al.**
    - This integrated analysis included 498 patients with CLL treated first-line with ibrutinib-based therapy or chlorambucil-based therapy with high-risk genomic features, including del(17p) and del(11q), unmutated IGHV, mutations in TP53, BIRC3, SF3B1, NOTCH1, or XPO1.
    - The median follow-up was 49.1 months (range, 0.1-78.7).
    - Ibrutinib-based therapy significantly improved ORR and PFS versus chlorambucil-based therapy.
    - At 42 months, PFS rates were significantly higher across high-risk genomic subgroups in ibrutinib-treated patients (63-82%) versus chlorambucil-treated patients (6-34%), and consistent PFS benefit with ibrutinib was observed across all high-risk genomic subgroups.
    - When comparing ibrutinib-treated pts with specified high-risk genomic features versus those without, PFS and ORR were comparable across different subgroups.
    - At a median treatment duration of 35.7-43.8 months, no meaningful difference was observed in the rate of AEs of any grade compared to the overall population.

Ibrutinib Induces Durable Remissions in Treatment-Naïve CLL Patients with 17p Deletion/TP53 Mutations: Five Year Follow-up from a Phase 2 Study [4]

- Results from the phase 2 study of treatment-naïve patients with deletion 17p/TP53 mutations treated with single-agent ibrutinib or ibrutinib in combination with rituximab were presented at ASH 2020 by **Sivina et al**.
    - Of the 27 treatment-naïve patients included, the median age was 62 years, 67% were male, 78% had unmutated IGHV, and 33% had advanced stage disease (Rai stage III-IV).
    - At a median follow-up of 61 months, median PFS and OS were not reached, and the estimated 5-year PFS and OS rates were 66% and 85%, respectively.
    - Objective responses were noted in all except one patient (ORR 96%), with CR in 10 (37%) patients, and PR in 16 (59%) patients.
        - Remission duration was not different in patients achieving CR or PR.
    - PD occurred in 6 patients, with a median time to progression of 39 months (range, 10-53).

Ibrutinib for Chronic Lymphocytic Leukemia with TP53 Alterations: 6 years of follow-up[5]

- Results from the Phase 2 PCYC-1122e study of first-line ibrutinib treatment in CLL patients with TP53 alterations were published by **Ahn et al** in the *New England Journal of Medicine*.
    - This study included 34 patients with CLL and TP53 alterations at a median age of 63 years.
    - At 6 years of follow-up, estimated PFS and OS were 61% (95% CI, 46-80) and 79% (95% CI, 67-94), respectively.
    - CR was achieved in 30% of patients.
    - At a median follow-up of 6.5 years, 17 patients (50%) remain on study, including 6 patients with a CR.
    - The safety profile was consistent with earlier reports of single-agent ibrutinib use and no new safety signals were reported.

In CLL/SLL with or without del(17p)/TP53 mutation:

- First-Line Therapy with del(17p)/TP53 mutation
- First-Line Therapy without del(17p)/TP53 mutation for:
    - *"Frail patient with significant comorbidity (not able to tolerate purine analogs) OR Patients aged ≥65 y and younger patients with significant comorbidities (CrCL <70 mL/min)*"
    - *"Patients aged <65 y without significant comorbidities"*

Rarity of B-Cell Receptor Pathway Mutations in Progression-Free Patients With Chronic Lymphocytic Leukemia (CLL) During First-Line Versus Relapsed/Refractory (R/R) Treatment With Ibrutinib [6]

- The objective of this study was to systematically evaluate the frequency and time to detection of *BTK* and *PLCG2* mutations in patients who were continuing to respond to ibrutinib (free of PD) in either 1L or R/R treatment. Results were presented at ASH 2020 by **Wiestner et al.**
- Peripheral blood samples were prospectively collected from 238 ibrutinib-treated in 1L (RESONATE-2, iLLUMINATE, and NCT01500733) and 150 patients in R/R settings (RESONATE and RESONATE-17)
    - With median testing follow-up of 35 months (range, 0-72) and 36 months (range, 1-69), the BTK mutation rates were 3% and 30% in previously untreated and R/R pts, respectively.
    - In the 1L and R/R settings, the rates of PLCG2 mutations were 2% and 7%, and the rates of co-occurring BTK/PLCG2 mutations were 1% and 5%, respectively.
    - Of the prespecified comparisons, there was superior freedom (P<0.001) from detection of BTK mutations in the following comparisons:
        - Patients treated with ibrutinib in the 1L vs R/R setting (HR 0.09; P<0.001; median time to detection was NR vs 58 months; 36-month mutation-free estimates: 99% versus 85%).

        - Patients in the overall population without versus with del(17p)/TP53 mutations (HR 0.31; P<0.001; 36-month mutation-free estimates: 98% versus 87%).
        - Patients treated in the R/R setting without versus with del(17p)/TP53 mutations (HR 0.27; P<0.001; 36-month mutation-free estimates: 93% versus 78%).
    - In addition, among all patients with del(17p)/TP53 mutations, improved freedom from BTK mutation was seen in previously untreated vs R/R pts (HR 0.09; P<0.001; 36-mo mutation-free estimates: 98% vs 78%).

In CLL/SLL without del(17p)/TP53 mutation:

- Relapsed/Refractory Therapy for:
    - *"Frail patient with significant comorbidity OR Patients aged ≥65 y and younger patients with significant comorbidities (CrCL <70 mL/min)"*
    - *"Patients aged <65 y without significant comorbidities"*

Phase 3 HELIOS Study: 5-year follow-up[7]

- Results from the final analysis of the Phase 3 HELIOS study of ibrutinib plus bendamustine and rituximab in patients with R/R CLL/SLL (n=578) were published by **Fraser et al**. in *Leukemia & Lymphoma*.
    - With this 5-year final analysis, the median follow-up was 63.7 months (range, 0.1-74.5; 95% CI 62.8-64.3) and the median time on treatment in the ibrutinib plus BR arm (n=287) was 55.7 months (range 0.2-72.9) versus 14.3 months in the placebo plus BR arm (n=287, treatment was discontinued at the interim analysis).
    - Median PFS for ibrutinib plus BR arm was 65.1 months versus 14.3 months in the placebo + BR arm. In addition, the 60-month PFS rate was 52.7% in the ibrutinib plus BR arm versus 8.2% in the placebo plus BR arm.
    - The OS advantage for patients in the ibrutinib plus BR arm versus placebo plus BR arm was maintained in this final analysis despite crossover of 183 (63.3%) patients (HR 0.611 [95% CI 0.455-0.822]; p=0.0010). Median OS was not reached in either group, however the 60-month OS rate was 75.7% for ibrutinib plus BR versus 61.2% for placebo plus BR.
    - Investigator-assessed ORR was 87.2% for ibrutinib plus BR versus 66.1% for placebo plus BR (p<.0001).
    - Rates of CR and CR with incomplete bone marrow recovery rate deepened over time, from 21.5% (62/289) at the interim analysis, to 38.1% (110/289) in the 3-year analysis, and 40.8% (118/289) in the final analysis.
    - Safety findings were consistent with known safety profiles of ibrutinib and BR in patients with CLL, and there were no unexpected findings at the latest follow-up analysis compared with the 3-year analysis.

References:

The following references are submitted with the full prescribing information[1] for your reference. 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® Prescribing Information.
2. Allan JN, Shanafelt T, Wiestner A, et al. Long-Term Efficacy of First-Line Ibrutinib Treatment for Chronic Lymphocytic Leukemia (CLL) With 4 Years of Follow-Up in Patients With TP53 Aberrations (del(17p) or TP53 Mutation): A Pooled Analysis From 4 Clinical Trials. *Blood.* 2020:Abstract 2219. https://ash.confex.com/ash/2020/webprogram/Paper134431.html
3. Burger JA, Robak T, Demirkan F, et al. Outcomes of First-Line Ibrutinib in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) and High-Risk Genomic Features with up

to 6.5 Years Follow-up: Integrated Analysis of Two Phase 3 Studies (RESONATE-2 and iLLUMINATE). *Blood.* 2020:Abstract 2220. https://ash.confex.com/ash/2020/webprogram/Paper134437.html
4. Sivina M, Jain N, Kim E, et al. Ibrutinib Induces Durable Remissions in Treatment-Naïve CLL Patients with 17p Deletion/TP53 Mutations: Five Year Follow-up from a Phase 2 Study. *Blood.* 2020:Abstract 2218. https://ash.confex.com/ash/2020/webprogram/Paper141014.html
5. Ahn IE, Tian X, Wiestner A. Ibrutinib for Chronic Lymphocytic Leukemia with TP53 Alterations. *New England Journal of Medicine.* 2020;383(5):498-500. https://www.nejm.org/doi/10.1056/NEJMc2005943?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed
6. Wiestner A, Ghia P, Byrd JC, et al. Rarity of B-Cell Receptor Pathway Mutations in Progression-Free Patients With Chronic Lymphocytic Leukemia (CLL) During First-Line Versus Relapsed/Refractory (R/R) Treatment With Ibrutinib. *Blood.* 2020:Abstract 2225. https://ash.confex.com/ash/2020/webprogram/Paper134386.html
7. Fraser GAM, Chanan-Khan A, Demirkan F, et al. Final 5-year findings from the phase 3 HELIOS study of ibrutinib plus bendamustine and rituximab in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leukemia & lymphoma.* 2020:1-10. https://doi.org/10.1080/10428194.2020.1795159

Sincerely,

Patrick Hardesty, PharmD, MS
Manager, Medical Communications
Pharmacyclics LLC, an AbbVie Company