May 15, 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: May 15, 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 Changes: Please find below requests for your consideration.

Indication		**Specific Request**
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 with del(17p)/TP53 mutation ***First-Line Therapy***		• Ibrutinib: Retain as a Preferred regimen
CLL/SLL without del(17p)/TP53 mutation ***Relapsed/Refractory 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 with del(17p)/TP53 mutation ***Relapsed/Refractory Therapy***		

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 (not able to tolerate purine analogs) OR Patients aged ≥65 y and younger patients with significant comorbidities (CrCL <70 mL/min)"*
- 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"*

In CLL/SLL with del(17p)/TP53 mutation:

- First-Line Therapy and Relapsed/Refractory Therapy

PCYC-1102/1103: Up to 8-Year Follow-Up

- Results from the final analysis of the Phase 1b/2 PCYC-1102 (NCT01105247) and PCYC-1103 extension study (NCT01109069) of single-agent ibrutinib in patients with treatment naïve (TN) CLL/SLL (n=31; age ≥65 years) or relapsed/refractory (R/R) CLL/SLL (n=101) were published by **Byrd et al.**[2]
- A summary of results as described by the authors is below:
  - Median follow-up was 87 months (range, 1–98) in the TN and 82 months (range, 0.7+ to 98) in the R/R settings, with up to 8 years of follow-up.
  - Median treatment duration was 75 months in the TN and 39 months in the R/R settings.
  - Overall response rate (ORR) was 87% in the TN and 89% in the R/R settings.
    - Complete response (CR) rate was 35% in the TN and 10% in the R/R settings.
    - Responses observed were durable, as the median duration of response was not reached in the TN setting and was 57 months in the R/R setting.
    - In R/R patients with del(17p), the ORR was 79% (27/34).
  - Depth of response improved over time in patients with initial PR-L, as 72/77 (94%) with initial PR-L later achieved a PR or better.
  - In the TN setting, median PFS and OS were not reached; the estimated 7-year PFS and OS rates were 83% and 84%, respectively. Of 31 TN patients, two experienced disease progression.
  - In the R/R setting, median PFS and OS were 52 months and 92 months, respectively; the estimated 7-year PFS and OS rates were 34% and 55%, respectively.
    - Median PFS and OS in the R/R setting trended longer for patients treated with fewer prior lines of therapy.
  - At a median follow-up of 85 months, no new serious AEs were noted, and the most frequently occurring grade ≥3 AEs were consistent with the previously published 5-year follow-up.[3]
    - The most frequent grade ≥3 AEs (>15% of all patients) were hypertension (n=37; 28%), pneumonia (n=32; 24%), and neutropenia (n=24; 18%).
    - Grade ≥3 AEs were most frequent in the first year and generally declined over time, except for hypertension; grade ≥3 AEs were also generally less frequent in TN than R/R patients, despite the longer median treatment duration for TN patients.

        - Sustained hematologic improvement in platelet counts, hemoglobin levels, and absolute neutrophil counts was observed in both TN and R/R patients with baseline cytopenia.
    - This final analysis of PCYC-1102/1103 provides the longest follow-up to date for single-agent ibrutinib across both the TN and R/R CLL settings.

BTKi and COVID-19:

- We would also like to provide for your awareness the following recent publications that discuss considerations for the use of BTK inhibitors (BTKi) in patients with COVID-19.
    - In **Treon, et al.**,[4] authors describe outcomes in 6 patients receiving ibrutinib for Waldenström's Macroglobulinemia, who were subsequently diagnosed with COVID-19.
    - In **Chong, et al.**,[5] authors present potential rationale both for and against continuation of BTKi in patients receiving BTKi therapy for B-cell malignancies who then develop COVID-19.

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; 2020. https://www.imbruvica.com/docs/librariesprovider7/default-document-library/prescribing-information.pdf.
2. Byrd JC, Furman RR, Coutre SE, et al. Ibrutinib Treatment for First-Line and Relapsed/Refractory Chronic Lymphocytic Leukemia: Final Analysis of the Pivotal Phase 1b/2 PCYC-1102 Study. *Clinical Cancer Research.* 2020:clincanres.2856.2019. https://clincancerres.aacrjournals.org/content/clincanres/early/2020/03/24/1078-0432.CCR-19-2856.full.pdf.
3. O'Brien S, Furman RR, Coutre S, et al. Single-Agent Ibrutinib in Treatment-Naïve and Relapsed/Refractory Chronic Lymphocytic Leukemia: A 5-Year Experience. *Blood.* 2018;131(17):1910-1919. https://ashpublications.org/blood/article-lookup/doi/10.1182/blood-2017-10-810044.
4. Treon SP, Castillo J, Skarbnik AP, et al. The BTK-inhibitor ibrutinib may protect against pulmonary injury in COVID-19 infected patients. *Blood.* 2020. https://ashpublications.org/blood/article/doi/10.1182/blood.2020006288/454437/The-BTKinhibitor-ibrutinib-may-protect-against.
5. Chong EA, Roeker LE, Shadman M, Davids MS, Schuster SJ, Mato AR. BTK inhibitors in cancer patients with COVID19: "The winner will be the one who controls that chaos" (Napoleon Bonaparte). *Clinical Cancer Research.* 2020:clincanres.1427.2020. https://clincancerres.aacrjournals.org/content/early/2020/04/28/1078-0432.CCR-20-1427.

Sincerely,

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