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NCCN Guidelines® Panel: Non-Hodgkin's Lymphomas

Dear NCCN,

Pharmacyclics, Inc. and Janssen Biotech, Inc. co-develop and co-commercialize IMBRUVICA® (ibrutinib) capsules. On behalf of Pharmacyclics Inc. and Janssen Biotech, Inc., I respectfully request the NCCN Guidelines® - Non-Hodgkin's Lymphomas Panel review the enclosed information for inclusion of ibrutinib for the treatment of patients with chronic lymphocytic leukemia (CLL) with a deletion of the short arm of chromosome 17 (del 17p).

Specific Request:

Recommend ibrutinib for the treatment of patients with CLL with del 17p.

- First-line CLL with del 17p: include as Category 1
- Relapsed/Refractory CLL with del 17p: upgrade to Category 1

A specific request was submitted to NCCN on 11-Jun 2014 to recommend ibrutinib for the treatment of relapsed or refractory (RR) CLL as a single agent (request to upgrade to Category 1) and in combination with an anti-CD20 antibody (Category 2) based on recent literature.

FDA Clearance:

On July 28, 2014 the U.S. Food and Drug Administration (FDA) granted full approval to IMBRUVICA® (ibrutinib) for patients with CLL who have received at least one prior therapy. The FDA also granted a new indication and full approval for patients with CLL with 17p deletion. Please refer to the IMBRUVICA® package insert for full indications and prescribing information.

US Prescribing Information:

In addition, the following sections of the IMBRUVICA® (ibrutinib) Prescribing Information were updated:

Section 1, Indications and Usage:

- 1.1 Mantle Cell Lymphoma (MCL)
- 1.2 Chronic Lymphocytic Leukemia (CLL)
- 1.3 CLL with 17p deletion

Section 5, Warnings and Precautions:

- 5.1 Hemorrhage

- 5.2 Infections
- 5.3 Cytopenias: Category changed from Myelosuppression to Cytopenias
- 5.4 Atrial Fibrillation ADDED and Renal Toxicity DELETED
- 5.5 Second Primary Malignancies

Section 6, Adverse Reactions

- 6.2 CLL: Updated with Phase 3 data (Study 2)

Section 7, Drug Interactions

- 7.2 CYP3A Inducers

Section 8, Use in Specific Populations

- 8.5 Geriatric Use

Section 12, Clinical Pharmacology

- 12.3 Pharmacokinetics
    - Absorption
    - Drug Interactions *Coadministration of Ibrutinib with CYP3A Inducers*

Section 14, Clinical Studies

- 14.2 CLL: Updated with Phase 3 data (Study 2)

Section 17, Patient Counseling Information

- Renal Toxicity (DELETED)
- Atrial Fibrillation (ADDED)
- Diarrhea

<u>Rationale for Request:</u>

On April 8, 2013, Pharmacyclics and Janssen announced that the U.S. Food and Drug Administration (FDA) granted a Breakthrough Therapy Designation for ibrutinib as a monotherapy in the treatment of patients with CLL or small lymphocytic lymphoma (SLL) with del 17p. On July 28, 2014, the FDA approved IMBRUVICA® (ibrutinib) for CLL patients with del 17p.

Single institution Phase 2 study[1-4]

An open-label, phase 2 study (NCT01500733) of ibrutinib 420 mg orally once daily in patients with CLL who have del 17p (15 treatment naïve [TN] and 14 RR) reported on the first 29 patients with a median follow-up of 9 months.[1,2] Ibrutinib was administered until disease progression or unacceptable toxicity. A nodal response (70% median reduction in lymph node size) was achieved in 88% of patients (n=25 evaluable) at 6 months (TN: 82% and RR: 93%). A partial response (PR) was achieved in 48% of patients by International Workshop on Chronic Lymphocytic Leukemia criteria, and a PR with lymphocytosis in an additional 40% of patients. The estimated event free survival at 12 months was 90%. One patient experienced progressive disease (presumed transformation). Grade 3 or higher non-hematologic toxicities occurred in 14% of patients, regardless of causality. The most common grade 1/2 adverse events (AEs) included: diarrhea, rash arthralgia, cramps, mouth sores, and fatigue. A total of 2 non-treatment related deaths occurred during the study.[1,2] The median lymph node response was 70%, median splenic volume reduction was 46%, and median bone marrow reduction in CD79a was 84% in del 17p patients, and was similar in patients in with non-del 17p.[3.4] In 20 del 17p patients who had repeat fluorescence in situ hybridization testing at 6 months, 80% had a relative decrease in size of their del 17p subclone (median reduction of 34%), including 4 patients who had no evidence of 17p.[3,4]

Pivotal accelerated approval study[5-10]:
Accelerated approval was based on a subset of RR CLL patients (n=48) treated with ibrutinib 420 mg daily in study PCYC-1102. PCYC-1102 is an open-label, multicenter, phase 1b/2 study (N=116; TN=31, RR=85) that was conducted to evaluate the safety and efficacy of ibrutinib 420 mg or 840 mg orally once daily in patients with CLL/SLL, including patients with del 17p (n=31; TN: n=2 and RR: n=29). Ibrutinib was administered until disease progression or unacceptable toxicity. The overall response rate (ORR) in patients with del 17p was 61%.[6] The ORR in the TN and RR del 17p populations were 100% [6,7] and 58.6% [6], respectively. In the RR del 17p group, the estimated progression-free survival (PFS) was 53.1%, and the estimated overall survival (OS) was 59.6%, at 26 months.[6] Responses in the TN and RR patients were independent of clinical and genomic risk factors, including 17p deletion.[6-8] Safety related outcomes were not reported separately for the del 17p subset; however, for the entire treatment population most AEs were grade ≤2 and the most commonly occurring AEs (≥20%) in TN and RR patients included diarrhea, nausea, upper respiratory tract infection, fatigue, cough, pyrexia, hypertension, peripheral edema, arthralgia, dizziness, dyspepsia, constipation, urinary tract infection, and vomiting. Hematologic toxicity ≥grade 3 was higher in RR patients than in TN patients.[6] An independent assessment of efficacy, 3 years following initiation of ibrutinib, demonstrated durability of response, and no new safety signals.[9,10] See full prescribing information for Warnings and Precautions, most common adverse reactions, and most common grade 3 or 4 adverse reactions.

Phase 3 data[11-13]:
RESONATE™ (PCYC-1112, N=391) is a randomized, multi-center, international, open-label, phase 3 study of single-agent ibrutinib versus the anti-CD20 antibody, ofatumumab, in patients with RR CLL or SLL. Ibrutinib was administered until disease progression or unacceptable toxicity. Ibrutinib demonstrated significant improvements in PFS by Independent Review Committee (IRC), and OS. Improvement in ORR by Investigator Assessment and by IRC was also observed. Improvements in PFS, OS and ORR were observed for the ibrutinib group of del 17p patients and are noted below.

Table: Efficacy in del17p Patients[11,12,14]

	Ibrutinib (n=63)	Ofatumumab (n=64)	Statistics
PFS[ab]	median not reached	5.8 months	HR for progression or death, 0.25; 95% CI, 0.14 to 0.45
ORR[c]	47.6% [d]	4.7%	

[a] Primary endpoint.
[b] At 6 months, 83% versus 49% of del17p patient were alive without progression in the ibrutinib versus ofatumumab groups.
[c] ORR by Independent Review Committee
Abbreviations: CI, confidence interval; del17p, deletion 17p; HR, hazard ratio; ORR, overall response rate; P, P-value; PFS, progression-free survival.

Safety was not summarized separately for del17p patients. Safety data for all 391 patients (n=163 ibrutinib; n=164 ofatumumab) are noted below. Treatment exposure was longer for ibrutinib (median 8.6 months, 0.2–16.1) compared with ofatumumab (median 5.3 months, 0–7.4); the cumulative AE profiles in at least 10% of patients were reported without adjustment for exposure duration. The most frequent (≥20%) all-grade non-hematologic AEs were diarrhea, fatigue, pyrexia, and nausea with ibrutinib, and fatigue, infusion-related reactions, and cough with ofatumumab. Grade ≥3 AEs occurring more frequently in patients receiving ibrutinib included diarrhea (4% vs 2%), nausea (2% vs 0%), pyrexia (2% vs 1%), neutropenia (16% vs 14%), thrombocytopenia (6% vs 4%), pneumonia (7% vs 5%), urinary

tract infection (4% vs 1%), and atrial fibrillation (3% vs 0%), with the latter AE requiring cessation of therapy in one patient. An additional four patients in the ibrutinib group and one patient in the ofatumumab group had grade 1-2 atrial fibrillation. Bleeding-related AEs of any grade were more common with ibrutinib than ofatumumab (44% vs 12%) and were most commonly petechiae, and included ecchymoses. Major hemorrhages (≥grade 3 or resulting in transfusion of red cells or hospitalization) were reported in two patients (1%) randomized to ibrutinib (including one patient with a subdural hematoma) and three patients (2%) receiving ofatumumab. AEs resulting in dose reduction occurred in 4% of patients treated with ibrutinib with only diarrhea leading to dose reduction in more than one patient (n=3). Treatment discontinuation due to AEs occurred in 4% of patients in each arm and fatal events occurred in 4% of patients who received ibrutinib and in 5% of patients who received ofatumumab.[11] See full prescribing information for Warnings and Precautions, most common adverse reactions, and most common grade 3 or 4 adverse reactions.

The following study publications and scientific congress presentations are submitted with the Full Prescribing Information.[14] We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

1) Wiestner A, Farooqui M, Valdez J et al. Single agent ibrutinib (PCI-32765) is highly effective in chronic lymphocytic leukemia patients with 17p deletion [abstract]. *Hematol Oncol.* 2013;31(suppl 1):98: Abstract 008. http://onlinelibrary.wiley.com/doi/10.1002/hon.2057/pdf. Accessed July 17, 2014.

2) Wiestner A. Single agent ibrutinib (PCI-32765) is highly effective in chronic lymphocytic leukemia patients with 17p deletion. Data presented at the *12th International Conference on Malignant Lymphoma*, June 19-22, 2013. Lugano, Switzerland.

3) Farooqui M, Aue G, Valdez J, et al. Single agent ibrutinib (PCI-32765) achieves equally good and durable responses in chronic lymphocytic leukemia (CLL) patients with and without del17p. *Blood.* 2013;122(21). Abstract 673. http://bloodjournal.hematologylibrary.org/content/122/21/673. Accessed July 17, 2014.

4) Farooqui M, Aue G, Valdez J, et al. Single agent ibrutinib (PCI-32765) achieves equal responses in CLL patients with and without 17p deletion. Data presented at the *American Society of Hematology 55th Annual Meeting*, December 7-10, 2013. New Orleans, LA.

5) Furman RR, O'Brien S, Flinn IW, et al. The Burton Tyrosine Kinase (BTK) inhibitor ibrutinib promotes a high frequency of durable response in relapsed/refractory and older treatment-naïve CLL patients: Final results of a Phase Ib/II study [abstract]. Presented at the XV International Workshop on Chronic Lymphocytic Leukemia (iwCLL), September 9-11, 2013. Cologne, Germany.

6) Furman RR, O'Brien S, Flinn IW, et al. The Burton Tyrosine Kinase (BTK) inhibitor ibrutinib promotes a high frequency of durable response in relapsed/refractory and older treatment-naïve CLL patients: Final results of a Phase Ib/II study [oral presentation]. Presented at the XV International Workshop on Chronic Lymphocytic Leukemia (iwCLL), September 9-11, 2013. Cologne, Germany.

7) O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. *Lancet Oncol.* 2014;15(1):48-58. Epub 2013 Dec 10.

8) Byrd JC, Furman RR, Coutre S, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2013;369(1):32-42.

9) O'Brien S, Furman RR, Coutre S, et al. Independent evaluation of ibrutinib efficacy 3 years post-initiation of monotherapy in patients with chronic lymphocytic leukemia/small lymphocytic leukemia including deletion 17p disease [abstract]. *J Clin Oncol*. 2014;32 (suppl):7014. http://meetinglibrary.asco.org/content/127270-144. Accessed July 17, 2014.

10) O'Brien S, Furman RR, Coutre S, et al. Independent evaluation of ibrutinib efficacy 3 years post-initiation of monotherapy in patients with chronic lymphocytic leukemia/small lymphocytic leukemia including deletion 17p disease [oral presentation]. Data presented at the *American Society of Clinical Oncology Annual Meeting*, May 31- June 3, 2014. Chicago, IL

11) Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med.* May 31 2014 [Epub ahead of print]. *N Engl J Med.* 2014;371(3):213-223.

12) Byrd JC, Brown JR, O'Brien S, et al. Randomized comparison of ibrutinib versus ofatumumab in relapsed or refractory chronic lymphocytic leukemia/ small lymphocytic lymphoma: Results from the phase III RESONATE™ trial [abstract]. *J Clin Oncol.* 2014;32 (suppl):7008. http://meetinglibrary.asco.org/content/129571-144. Accessed July 17, 2014.

13) Byrd JC, Brown JR, O'Brien S, et al. Randomized comparison of ibrutinib versus ofatumumab in relapsed or refractory chronic lymphocytic leukemia/ small lymphocytic lymphoma: Results from the phase III RESONATE™ trial [oral presentation]. Presented at the 50th Annual Meeting of the American Society of Clinical Oncology, May 30-June 3, 2014, Chicago, IL. Abstract 7008.

14) IMBRUVICA® (ibrutinib) capsules [package insert]. Sunnyvale, CA: Pharmacyclics, Inc. 07/2014

Sincerely,

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Pharmacyclics, Inc.