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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 updated data for inclusion of IMBRUVICA (ibrutinib) for the treatment of patients with relapsed/refractory (RR) chronic lymphocytic leukemia (CLL).

Specific Change:

Recommend IMBRUVICA (ibrutinib) for the treatment of patients with RR CLL for each of the following treatment options:

- Single-agent therapy: upgrade to Category 1
- Combination therapy with an anti-CD20 antibody: Category 2

Please consider the following recommendations based upon two publications of single-agent ibrutinib in the New England Journal of Medicine (Phase 1b/2 study PCYC-1102, and Phase 3 study PCYC-1112 RESONATE™), as well as oral/poster presentations of three ibrutinib combination studies at the American Society of Hematology 2013 and American Society of Clinical Oncology 2014 meetings.

FDA Clearance:

The U.S. Food and Drug Administration (FDA) approved IMBRUVICA (ibrutinib) for the treatment of patients with CLL who have received at least one prior therapy, and for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. The accelerated approvals for these indications are based on overall response rate (ORR). Please refer to the IMBRUVICA full prescribing information for additional details.

On April 8, 2014, Pharmacyclics submitted a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA), based on data from the randomized, multi-center, open-label, phase 3 study PCYC-1112, RESONATE, which compared single-agent ibrutinib with ofatumumab in patients with CLL or small lymphocytic lymphoma (SLL), who had received at least one prior therapy. At a planned interim analysis in January 2014, the results of this study demonstrated a statistically significant improvement in progression-free survival (PFS)(primary endpoint) in patients treated with ibrutinib, as well as a statistically significant improvement in overall survival (OS)(secondary endpoint). On June 9, 2014, Pharmacyclics announced that the FDA accepted this sNDA filing to support the review

of an application for full approval. The Prescription Drug User Fee Act (PDUFA) date for FDA's review of this application is October 7, 2014 .

Rationale:

Data as a single agent:

Phase 3 data¹:

A randomized, multi-center, international, open-label, phase 3 study (PCYC-1112, RESONATE, N=391) of single-agent ibrutinib versus (vs) the anti-CD20 antibody, ofatumumab, in patients with RR CLL/SLL demonstrated a significant improvement in PFS and OS by Independent Review Committee (IRC). Improvements in PFS and OS were observed irrespective of baseline clinical characteristics or molecular features. Improvement in ORR by Investigator Assessment and by IRC was also observed.

Table: Efficacy Endpoints at a Median Follow-up of 9.4 Months (range, 0.1 to 16.6)¹

	Ibrutinib (n=195)	Ofatumumab (n=196)	Statistics
PFS^a	median not reached	8.1 months	HR for progression or death, 0.22; 95% CI, 0.15 to 0.32; P<0.001
OS	median not reached ^b	median not reached	HR for death, 0.43; 95% CI, 0.24 to 0.79; P=0.005
ORR^c	70% ^d	22%	
^a Primary endpoint. ^b 57 ofatumumab patients were initiated on ibrutinib in cross-over after confirmed progression. ^c Investigator Assessed. ORR by Independent Review Committee was 43% vs 4% for ibrutinib vs ofatumumab; P<0.001 ^d An additional 15% of ibrutinib-treated patients achieved a partial response with lymphocytosis. Abbreviations: CI, confidence interval; HR, hazard ratio; ORR, overall response rate; OS, overall survival; P, P-value, PFS, progression-free survival.			

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 adverse event (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. 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. Adverse events 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 5% of patients who received respectively, for ibrutinib and ofatumumab.¹

Pivotal accelerated approval study²:

Results from an open-label, multi-center, Phase 1b/2 study (PCYC-1102, N=85) were previously submitted to the Non-Hodgkin's Lymphomas NCCN Guidelines® Panel for review in February 2014, and have since been reflected in the Guidelines®.

Long-term follow-up^{3,4}:

Study PCYC-1102 included the patients with RR CLL/SLL noted in Byrd NEJM 2013 (n=85), a food-effect CLL/SLL cohort (n=16), and patients with treatment naïve (TN) CLL/SLL noted in O'Brien Lancet 2013 (n=31). An independent assessment of efficacy, 3 years following initiation of ibrutinib, demonstrated durability of response. The median time on study for all 132 patients was 29.4 months (range, 0.7-38.1). The updated ORR, by IRC, was 78% for all-treated patients (83.9% TN, 76.2% RR, and 55.9% RR with del 17p). Ninety-two percent of patients who achieved a partial response with lymphocytosis (PR-L) converted to a better response over time. The median duration of response was not reached for all-treated patients. No new safety signals were observed in long-term follow-up; 64% of patients remain on treatment with ibrutinib.^{3,4}

Data in combination with an anti-CD20 antibody:

- Ibrutinib plus ofatumumab in patients with RR CLL/SLL and related diseases^{5,6}
- Ibrutinib plus rituximab in patients with high-risk CLL/SLL^{7,8}
- Ibrutinib plus rituximab and bendamustine in patients with RR CLL/SLL^{9,10}

Results from an open-label, non-randomized, phase 1b/2 safety and efficacy study (PCYC-1109) of ibrutinib 420 mg orally once daily, in 28-day cycles combined with ofatumumab in three different administration sequences in patients with RR CLL/SLL (n=66), prolymphocytic leukemia (PLL) (n=2) and Richter's transformation (RT) (n=3), reported an ORR of 100% (1 cycle of ibrutinib with addition of ofatumumab in cycle 2), 79% (ibrutinib plus ofatumumab concomitantly), and 71% (2 cycles of ofatumumab with additional of ibrutinib starting in cycle 3). At 12 months, PFS was 89%, 85%, and 75% in the respective cohorts. The most frequently reported AEs (>25%) were diarrhea (68%), infusion-related reactions (45%), peripheral sensory neuropathy (42%), stomatitis (37%), contusion (27%), and upper respiratory infection (25%). The most common grade 3 or 4 AE was neutropenia (23%). Seventy-six percent of patients continued ibrutinib in a long-term extension study.^{5,6}

Updated results from an open-label, single-center, phase 2 study (NCT01520519, N=40) evaluated the safety and efficacy of ibrutinib 420 mg orally once daily in combination with rituximab in patients with high-risk CLL (del 17p or TP53 mutation, or short PFS <36 months after frontline chemo-immunotherapy, or relapsed CLL with del 11q). At 12 months or best response before study discontinuation, the ORR was 95%. A complete response was reported for 4 patients; 1 patient became minimal residual disease negative. At 18 months, the median PFS was 78% and the OS was 84%. Grade 3 toxicities related to therapy included lung infection, peripheral neuropathy, neutropenia, eye disorder/mucositis, and alanine aminotransferase increase. Nine patients discontinued therapy, including 3 due to infection, 2 due to progressive disease, and 1 due to RT.^{7,8}

Final results from a multi-center, open-label, phase 1b study (PCYC-1108, N=30) evaluating the safety and efficacy of ibrutinib 420 mg orally once daily in combination with bendamustine and rituximab in patients with RR CLL, reported an ORR of 93.4% (CR: 16.7%, nodal PR: 10% and PR: 66.7%). Responses were reported independent of high-risk clinical or genomic features, and were associated with improved hemoglobin and platelet counts. At a median follow-up of 15.8 months, the median PFS has not been reached. The estimated 12-month PFS was 90%. Grade 3/4 hematologic AEs included neutropenia

(40%), febrile neutropenia (7%), and thrombocytopenia (7%). Grade 3 non-hematologic AEs (≥2 patients) included rash (10%), fatigue (10%), and cellulitis (7%). No discontinuations related to death or AEs were reported. Seventy percent of patients continue on long-term treatment, and an additional 17% proceeded to stem cell transplant.^{9,10}

The following study publications are submitted with the full Prescribing Information.¹¹ 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) Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphocytic leukemia. *N Engl J Med*. May 31 2014 [Epub ahead of print].
- 2) 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.
- 3) 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>
- 4) 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
- 5) Jaglowski SM, Jones JA, Flynn JM, et al. A phase Ib/II study evaluating activity and tolerability of BTK inhibitor ibrutinib in combination with ofatumumab in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and related diseases [abstract]. *J Clin Oncol*. 2014;32 (suppl):7009. <http://meetinglibrary.asco.org/content/132436-144>
- 6) Jaglowski S, Jones J, Flynn J, et al. A phase Ib/II study evaluating activity and tolerability of BTK inhibitor ibrutinib in combination with ofatumumab in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and related diseases. Data presented at the *American Society of Clinical Oncology Annual Meeting*, May 31- June 3, 2014. Chicago, IL.
- 7) Burger JA, Keating MJ, Wierda WG, et al. Ibrutinib in combination with rituximab (iR) is well tolerated and induces a high rate of durable remissions in patients with high-risk chronic lymphocytic leukemia (CLL): new, updated results of a phase II trial in 40 patients [abstract]. *Blood* 2013; 122(21):675. <http://bloodjournal.hematologylibrary.org/content/122/21/675>
- 8) Burger JA, Keating MJ, Wierda WG, et al. Ibrutinib in combination with rituximab (iR) is well tolerated and induces a high rate of durable remissions in patients with high-risk chronic lymphocytic leukemia (CLL): new, updated results of a phase II trial in 40 patients. Data to be presented at the *American Society of Hematology 55th Annual Meeting*, December 7-10, 2013. New Orleans, LA.

- 9) Brown JR, Barrientos JC, Barr PM, et al. Ibrutinib in combination with bendamustine and rituximab is active and tolerable in patients with relapsed/refractory CLL/SLL: final results of a phase 1b study [abstract]. *Blood* 2013;122 (21); 525.
<http://bloodjournal.hematologylibrary.org/content/122/21/525>
- 10) Brown JR, Barrientos JC, Barr PM, et al. Ibrutinib in combination with bendamustine and rituximab is active and tolerable in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic leukemia: final results of a phase 1b study. Data presented at the *American Society of Hematology Annual Meeting*, December 7-10, 2013. New Orleans, LA.
- 11) IMBRUVICA® (ibrutinib) capsules [package insert]. Sunnyvale, CA: Pharmacyclics, Inc. 02/2014
- 12) 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 [abstract]. *Blood* 2013; 122(21):673.
<http://bloodjournal.hematologylibrary.org/content/122/21/673>
- 13) 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. Data presented at the *American Society of Hematology 55th Annual Meeting*, December 7-10, 2013. New Orleans, LA.

Sincerely,



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