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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 updated and enclosed data for inclusion of IMBRUVICA (ibrutinib) for the initial treatment of elderly patients with chronic lymphocytic leukemia (CLL).

Specific Change:

Recommend IMBRUVICA (ibrutinib) for the first-line treatment of elderly patients with CLL.

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). Improvements in survival or disease-related symptoms have not been established. Please see full prescribing information for more details.

Rationale:

An open-label, multi-center, phase 1b/2 study (PCYC-1102, N=31) was conducted to evaluate the safety and efficacy of ibrutinib 420 mg and 840 mg orally once-daily in treatment naïve (TN) patients with CLL or small lymphocytic lymphoma (SLL). Baseline patient characteristics included: median age 71 years (range 65-84); Rai stage III/IV, 54%; bulky nodes ≥5 cm, 19%; unmutated immunoglobulin variable-region heavy-chain gene, 48%; beta-2-microglobulin >3 mg/L, 26%; and non-methylated ZAP-70, 52%. Ibrutinib was administered until disease progression or unacceptable toxicity. The ORR, as measured by the modified International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria and per investigator report, was 71% (17 partial responses [PRs], 4 complete responses [CRs]) and 1 nodular PR). Additionally, a PR with persistent lymphocytosis was reported for 4 patients (13%). The response was independent of clinical and genomic risk factors present before treatment, including age, advanced-stage disease, bulky disease, cytopenias, the 17p13.1 deletion, the 11q22.3 deletion, ZAP-70 methylation, and beta-2-microglobulin level. The median progression free survival (PFS) was not reached, with only one patient progressing during follow-up. The 24-month PFS was 96.3% (95% confidence interval: 76.5-99.5). Sustained hematologic improvement was observed in 7 of 12 patients with baseline thrombocytopenia (58%) and 7 of 11 patients with baseline anemia (64%). The

most commonly occurring adverse events (AEs) in >25% of patients were: diarrhea (68%), nausea (48%), fatigue (32%), hypertension 29%, peripheral oedema (29%), dizziness (26%), dyspepsia (26%), and upper respiratory tract infection (26%). Grade 3 or 4 hematologic toxicity included 1 case of thrombocytopenia (3%) and 1 case of neutropenia (3%). No bleeding AEs ≥grade 2 were reported. Three patients had infections (grade 3) and two patients discontinued treatment due to AEs (grade 3 fatigue and grade 2 viral infection).[1]

The long term safety and durability of responses for patients in study PCYC-1102 were presented at the 50th Annual Meeting of the American Society of Clinical Oncology in Chicago, IL.[2,3] The median time on study was 32.1 months (range, 2.5–38.1) for the TN patients (n=31). The ORR in these patients was 81% by investigator assessment and 84% by Independent Review Committee, with a concordance of 97%. The median duration of response was not reached (range, 0-35+ months) and 81% of TN patients remained on ibrutinib therapy. One patient (3%) discontinued treatment for progressive disease and 3 patients (10%) discontinued treatment due to AEs.[2,3]

An open-label, phase 2 study (NCT01500733) of ibrutinib 420 mg orally once-daily in patients with CLL/SLL who have deletion of the short arm of chromosome 17 (del 17p) reported on the first 29 patients (15 TN and 14 relapsed/refractory [RR]) with a median follow-up of 9 months. Baseline patient characteristics included: age 33-83 years; Rai stage ≥3, 66%; bulky disease, 52%; and splenomegaly, 62%. A nodal response (70% median reduction in lymph node size) was achieved in 88% of patients (25/29 evaluable) at 6 months (TN: 82% and RR: 93%). In the overall population, a PR was achieved in 48% of patients by iwCLL criteria, and a PR with lymphocytosis was achieved in an additional 40% of patients. The estimated PFS at 15 months was 87% for TN and 85% for RR patients. One patient experienced progressive disease (presumed transformation). Grade 3 or higher non-hematologic toxicities were reported in 13% of patients, regardless of causality. The most common grade 1/2 AEs included: diarrhea, rash, arthralgia, cramps, mouth sores, and fatigue. A total of 2 non-treatment-related deaths occurred during the study. No discontinuations due to AEs were reported. Hematologic AEs were reported as rare.[4,5]

The following study publications are submitted with the full Prescribing Information.[6] 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) O'Brien S, Furman RR, Coutre SE, et al. Iburtinib 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.

2) O'Brien S, Furman R, Coutre S, et al. Independent evaluation of ibrutinib efficacy 3 year post-initiation of monotherapy in patients with chronic lymphocytic leukemia/small lymphocytic leukemia including deletion 17p disease [oral presentation]. Presented at the 50th Annual Meeting of the American Society of Clinical Oncology, May 30 – June 3, 2014, Chicago, IL. Abstract 7014. http://meetinglibrary.asco.org/content/127270-144

3) O'Brien S, Furman R, Coutre S, et al. Independent evaluation of ibrutinib efficacy 3 year post-initiation of monotherapy in patients with chronic lymphocytic leukemia/small lymphocytic leukemia including deletion 17p disease [abstract]. *J Clin Oncol.* 2014;32(5S):abstract 7014.

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

5) Wiestner A, Farooqui M, Valdez J, et al. Single agent ibrutinib (PCI-32765) is highly effective in chronic lymphocytic leukemia patients with 17p deletion [oral presentation]. Presented at the 12th International Conference on Malignant Lymphoma, June 19-22, 2013, Lugano, Switzerland. Abstract 008

6) IMBRUVICA® (ibrutinib) capsules [package insert]. Sunnyvale, CA: Pharmacyclics, Inc. 02/2014

Sincerely,

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