

November 13, 2013

Name: Lisa Ambrose, RPh, PharmD-c, BCOP
Company/Organization: Janssen Biotech, Inc.
Address: 850 Ridgeview Drive Horsham, PA 19044
Phone: 804.539.7417
E-mail: Lmeadows@its.jnj.com
Date of request: November 13, 2013
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 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,
- Combination therapy with bendamustine and rituximab,
- Combination therapy with ofatumumab, AND
- Combination therapy with rituximab

FDA Clearance:

The FDA has approved IMBRUVICA™ (ibrutinib) for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established.

Rationale:

An open-label, multicenter, phase 1b/2 study (PCYC-1102, N=85) was conducted to evaluate the safety and efficacy of ibrutinib 420 mg (n=51) and 840 mg (n=34) orally once daily in patients with RR CLL or small lymphocytic lymphoma (SLL). The overall response rates (ORR) were as follows: 420 mg cohort: 71% (34 partial responses [PRs], 2 complete responses [CRs]) and 840 mg cohort: 71% (24 PRs). A PR with persistent lymphocytosis was noted for 10 patients (20%) in the 420 mg cohort and 5 patients (15%) in the 840 mg cohort. The response was independent of clinical and genomic risk factors present before treatment, including advanced-stage disease, the number of previous therapies, and the 17p13.1 deletion. Sustained improvement of platelet counts (>100,000 cells per cubic millimeter without growth factors or need for transfusion for at least 2 cycles), hemoglobin (>50% increase or level > 11 grams per deciliter), and neutropenia (absolute neutrophil count > 1500 cells per cubic millimeter) were observed in 32 of 41 patients with baseline thrombocytopenia (78%), 27 of 33 patients with anemia (82%), and 24 of 31 patients with neutropenia (77%), respectfully. Most adverse events (AEs) were grade ≤2, with the

most commonly occurring AEs (>30%) to include: diarrhea (49%), upper respiratory tract infection (33%), fatigue (32%), and cough (31%). Hematologic toxicity grade 3 or 4 occurred infrequently and included neutropenia (15%), thrombocytopenia (6%), and anemia (6%). Bleeding AEs \geq grade 3 were reported in 4 out of 85 patients. The average infection rate during the first 6 months was 7.1 per 100 patient-months [PM] and decreased to 2.6 per 100 PM thereafter. Two patients in the 420 mg cohort and 4 patients in the 840 mg cohort discontinued treatment due to AEs.¹

A multicenter, open-label, phase 1b/2 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 90% (CR: 10% and PR: 80%) at 8.1 months median follow-up. Responses were reported independent of high-risk clinical or genomic features. Grade 3/4 AEs included neutropenia (47%) and thrombocytopenia (10%). Grade 3 nonhematologic AEs potentially related to ibrutinib included rash (3 patients) and fatigue, tumor lysis, and cellulitis in 2 patients each. No grade 4 non-hematologic AEs or discontinuations related to death or AEs were reported.^{2,3}

Interim data from an ongoing, 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 patients with RR CLL/SLL (n =24) and Richter's transformation (RT) (n=3), reported an ORR of 100% in RR CLL/SLL and 67% with RT (all responses were PR). No grade 3 or 4 infusion reactions, neutropenia, or thrombocytopenia were reported at a median follow-up of 9.8 months. The majority of AEs were grade 1/2. Grade 3/4 AEs included anemia (11%), pneumonia (11%), urinary tract infection (7%), and hyponatremia (7%).^{4,5}

An open-label, single-center, phase 2 study (NCT01520519, N=40) evaluated the safety and efficacy associated with the combination of ibrutinib 420 mg orally once daily and rituximab in high-risk CLL (del 17p or TP53 mutation, or short progression free survival [PFS] <36 months after frontline chemo-immunotherapy, or relapsed CLL with del 11q) patients. A total of 37 out of 40 patients continued on therapy without disease progression at a median follow-up of 8 months. A CR was reported for 4 patients and 30 achieved PR with an ORR of 85%. Also, 2 PRs were reported with persistent lymphocytosis and 3 patients achieved stable disease. Six patients experienced grade 3/4 toxicities with therapy which included anemia, mucositis, febrile neutropenia, and pneumonia. Grade 1/2 toxicities which were mostly self-limited included diarrhea, myalgias/bone pains, fatigue, upper respiratory tract infections, bruising, and hot flashes. Relapse occurred in 1 patient who initially responded and 2 patients died from unrelated infections.^{6,7}

The following study publications are submitted with the Full Prescribing Information.⁸ 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, Furman RR, Coutre S, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369(1):32-42.
- 2) O'Brien SM, Barrientos JC, Flinn IW, et al. Combination of the Bruton's tyrosine kinase (BTK) inhibitor PCI-32765 with bendamustine (B)/rituximab (R) (BR) in patients (pts) with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): Interim results of a phase Ib/II study [abstract]. *J Clin Oncol*. 2012;30(suppl):6515.

- 3) O'Brien S, Barrientos J, Flinn I, et al. Combination of the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765) with bendamustine /rituximab is active and tolerable in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): Interim results of a phase Ib/II study. Data presented at the *American Society of Clinical Oncology Annual Meeting*, June 1-5, 2012. Chicago, IL.
- 4) Jaglowski SM, Jones JA, Flynn JM, et al. A phase Ib/II study evaluating activity and tolerability of BTK inhibitor PCI-32765 and ofatumumab in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and related diseases [abstract]. *J Clin Oncol*. 2012;30(suppl):6508.
- 5) Jaglowski S, Jones J, Flynn J, et al. A phase Ib/II study evaluating activity and tolerability of BTK inhibitor PCI-32765 and 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*, June 1-5, 2012. Chicago, IL.
- 6) Burger JA, Keating MJ, Wierda WG, et al. Efficacy and safety of ibrutinib in combination with rituximab in high-risk CLL patients [abstract]. *Hematol Oncol*. 2013;31(suppl 1):193:292.
- 7) Burger JA, Keating MJ, Wierda WG, et al. Efficacy and safety of ibrutinib in combination with rituximab (iR) in high-risk CLL patients. Poster presented at: 12th International Conference on Malignant Lymphoma, June 19-22, 2013, Lugano, Switzerland. Poster 292.
- 8) IMBRUVICA™ (ibrutinib) capsules [package insert]. Sunnyvale, CA: Pharmacyclics, Inc.
- 9) O'Brien S, Furman RR, Fowler N, et al. The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765) monotherapy demonstrates long-term safety and durability of response in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) patients in an open-label extension study. Poster to be presented at: The American Society of Hematology 55th Annual Meeting, December 7-10, 2013. New Orleans, LA.
- 10) 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 to be presented at the *American Society of Hematology 55th Annual Meeting*, December 7-10, 2013. New Orleans, LA.
- 11) 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.
- 12) 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. Poster to be presented at: The American Society of Hematology 55th Annual Meeting, December 7-10, 2013. New Orleans, LA.

Sincerely,

Lisa Meadows Ambrose, RPh, PharmD-c, BCOP
Therapeutic Manager, Oncology Medical Information
Janssen Scientific Affairs, LLC