

November 13, 2013

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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 chronic lymphocytic leukemia (CLL) who demonstrate deletion of the short arm of chromosome 17 (del 17p).

Specific Change:

Recommend IMBRUVICA™ (ibrutinib) for the treatment of patients with CLL with del 17p.

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:

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.

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 relapsed/refractory [RR]) reported on the first 29 patients with a median follow-up of 9 months. 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 IWCLL 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}

An open-label, multicenter, phase 1b/2 study (PCYC-1102, N=116) was conducted to evaluate the safety and efficacy of ibrutinib 420 mg orally once daily in patients with CLL, including patients with del 17p (n=30). The overall response rate (ORR) in patients with del 17p was 67%. The ORR in the TN and relapsed/refractory (RR) del 17p population were 100% (n=2) and 68% (n=28), respectively. In the RR del 17p group, the estimated progression-free survival (PFS) was 57%, and the estimated overall survival (OS) was 70%, at 26 months. Safety related outcomes were not reported for the del 17p subset; however, for the entire treatment population most AEs were grade ≤2 with the most commonly occurring AEs to include: diarrhea (54%), upper respiratory tract infection (29%), fatigue (29%), rash (28%), nausea (26%), and arthralgias (25%). Hematologic toxicity ≥grade 3 was relatively infrequent.^{3,4}

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 patients, including those with del 17p (n=20). Efficacy and safety outcomes were not reported for the del 17p subset; however, a total of 37 out of 40 patients continued on therapy without disease progression at a median follow-up of 8 months. The ORR was 85% and included 4 patients who achieved a complete response (CR) and 30 patients who achieved a PR. Also, 2 PRs were reported with persistent lymphocytosis and 3 patients achieved SD (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.^{5,6}

A multicenter, open-label, phase 1b/2 study (PCYC-1108, N=30) evaluating the safety and efficacy of ibrutinib 420 mg orally once daily combined with bendamustine and rituximab in patients with RR CLL, reported an ORR of 71% and a CR of 14% in 7 patients with del 17p at 8.1 months median follow-up. Safety related outcomes were not reported for the del 17p subset; however, grade 3/4 AEs for the entire treatment population included neutropenia (47%) and thrombocytopenia in (10%). Grade 3 non-hematologic 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.^{7,8}

The following study publications are submitted with the Full Prescribing Information.⁹ 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):98:008.
- 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) Byrd JC, Furman RR, Coutre S, et al. The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765) promotes high response rate, durable remissions, and is tolerable in treatment naïve (TN) and relapsed or refractory (RR) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) patients including patients with high-risk disease: new and updated results of 116 patients in a phase Ib/II study [abstract]. *Blood*. 2012;120(21):189.

- 4) Byrd JC, Furman R, Coutre S, . The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765) promotes high response rate, durable remissions, and is tolerable in treatment naïve (TN) and relapsed or refractory (RR) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) patients including patients with high-risk disease: new and updated results of 116 patients in a phase Ib/II study. Data presented at the *American Society of Hematology 54th Annual Meeting*, December 8-11, 2012. Atlanta, GA.
- 5) 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.
- 6) 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: The 12th International Conference on Malignant Lymphoma, June 19-20, 2013. Lugano, Switzerland. Poster 292.
- 7) 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.
- 8) 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.
- 9) IMBRUVICA™ (ibrutinib) capsules [package insert]. Sunnyvale, CA: Pharmacyclics, Inc.
- 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,

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