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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 data for inclusion of IMBRUVICA™ (ibrutinib) for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Specific Change: Recommend IMBRUVICA™ (ibrutinib) for the treatment of patients with previously treated MCL.

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 November 13, 2013, Pharmacyclics and Janssen announced that the U.S. Food and Drug Administration (FDA) has approved IMBRUVICA™ (ibrutinib) for the treatment of patients with MCL who have received at least one prior therapy. This comes after the FDA granted a Breakthrough Therapy Designation for ibrutinib as a monotherapy in the treatment of patients with relapsed/refractory (RR) MCL earlier this year.

A phase 2, open-label, international study (PCYC-1104) investigated the efficacy and safety of ibrutinib 560 mg orally once daily until disease progression or unacceptable toxicity in patients with RR MCL, including bortezomib-naïve (<2 complete cycles or no prior bortezomib) and bortezomib-exposed

(≥ 2 cycles) patients (N=115). The overall response rate (ORR) was 68% (complete response rate [CR]: 21% and partial response [PR] rate: 47%). The response rates did not vary based on prior exposure to bortezomib (ORR: 67% bortezomib-exposed vs. 68% bortezomib-naïve). Median time to PR and CR were 1.9 months (range, 1.4-13.7 months) and 5.5 months (range, 1.7-11.5 months), respectively, with an estimated median duration of response of 17.5 months. The estimated median progression-free survival (PFS) was 13.9 months (range, 0.7 to 21.4). The estimated median overall survival (OS) had not been reached; however, the OS was estimated to be 58% at 18 months. The most common non-hematologic adverse events (AEs) occurring in >20% of patients included: diarrhea (50%), fatigue (41%), nausea (31%), peripheral edema (28%), dyspnea (27%), constipation (25%), upper respiratory tract infection (23%), vomiting (23%), and decreased appetite (21 %). Grade 3 and 4 hematologic AEs included neutropenia (16%), thrombocytopenia (11%), and anemia (10%). Pneumonia (6%) was the most common infection ≥grade 3. Subdural hematomas were reported in 4 patients which were all associated with falls, head trauma, or both. Additionally, all 4 patients were receiving either aspirin or warfarin within 2 days before or on the date of the bleeding event. Five patients experienced grade 3 bleeding events which included subdural hematomas (2%), hematuria (2%), and lower gastrointestinal hemorrhage (1%). Eight patients (7%) discontinued therapy due to an AE.[1] An update to this study was presented at the 12th Internal Conference on Malignant Lymphoma in Lugano, Switzerland.[2]

The following study publications are submitted with the Full Prescribing Information.[3] 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) Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *New Engl J Med*. 2013;369(6):507-516.

2) Wang ML, Rule S, Martin P, et al. Updated interim results of an international, multicenter, phase 2 study of ibrutinib (PCI-32765) in relapsed or refractory mantle cell lymphoma [abstract]. *Hematol Oncol*. 2013;31(suppl 1):194:293.

3) IMBRUVICA™ (ibrutinib) capsules [package insert]. Sunnyvale, CA: Pharmacyclics, Inc.

Sincerely,

Lisa Meadows Ambrose RPh, PharmD-c, BCOP

Therapeutic Manager, Oncology Medical Information

Janssen Scientific Affairs, LLC