January 29, 2015

Name: Joi Ninomoto, RPh, PharmD
Company/Organization: Pharmacyclics, Inc.
Address: 995 East Arques Avenue, Sunnyvale, CA 94085
Phone: 408.218.3089
E-mail: jninomoto@pcyc.com
Date of request: January 29, 2015
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) in combination with rituximab for the treatment of patients with relapsed/refractory (RR) mantle cell lymphoma (MCL).

FDA Clearance:

IMBRUVICA® (ibrutinib) is indicated for the treatment of patients with MCL who have received at least one prior therapy. Accelerated approval was granted for this indication based on overall response rate (ORR). Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials. IMBRUVICA® is also indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, and for the treatment of patients with CLL with deletion 17p.

On January 29, 2015, the U.S. Food and Drug Administration granted IMBRUVICA® regular full approval for the treatment of patients with Waldenström's Macroglobulinemia. Please refer to the IMBRUVICA® package insert for complete information about the use of IMBRUVICA® in its approved indications.

Specific Change:

Recommend addition of IMBRUVICA® (ibrutinib) in combination with rituximab for the treatment of patients with RR MCL.

Rationale for request to add MCL combination information:

Ibrutinib was approved by the US Food and Drug Administration as a single agent for MCL patients who received at least one prior therapy based on a Phase 2 clinical trial (N=111) which demonstrated an overall response rate (ORR) of 65.8% (17.1% complete response [CR]; 48.6 partial response [PR]). The median duration of response (DOR) was 17.5 months (95% confidence interval of 15.8 months to not reached).[1] This study was published by Wang et al.[2]

In a single-center Phase 2 study of ibrutinib in combination with rituximab (iR) in previously treated MCL patients (median of 3 prior therapies [range, 1-9]) (N=50), the ORR was 88% (40% CR and 48% PR).[3,4] With a median follow-up of 11 months (range 4-16 months), the median DOR and progression-free

survival have not been reached. For the subset of patients with Ki67 < 50% (n=34), the ORR was 100% (56% CR). The most common (>20%) treatment-emergent adverse events (TEAEs) included fatigue, diarrhea, myalgia, dyspnea, oral mucositis, dizziness, dry eye, blurred vision, peripheral sensory, anemia, thrombocytopenia, memory impairment, nausea, and limb edema. Most of these events were grade 1 or 2. Grade 3-4 TEAEs included leukocytosis, neutropenia, thrombocytopenia, atrial fibrillation, diarrhea and fatigue. Twenty-two patients came off study, including 2 who withdrew consent for combination iR but remained on single agent ibrutinib, 3 for toxicity, 10 for progressive disease[all had Ki67 > 50%], 2 secondary malignancies, and 5 who went on to stem cell transplant.

US Prescribing Information:

Major changes to the USPI include addition of WM as a new indication, along with WM safety and efficacy data. Tumor Lysis Syndrome was added to the Warnings & Precautions. In addition, the following sections of the IMBRUVICA® (ibrutinib) Prescribing Information were updated and are noted below, as they may affect treatment and management of MCL patients. This list does not include all changes to the revised IMBRUVICA® USPI, please see the enclosed full prescribing information.

Section 1, Indications and Usage:
- 1.1 Mantle Cell Lymphoma (accelerated approval language updated)

Section 2, Dosage and Administration:
- 2.5 Dose Modifications for Use in Hepatic Impairment (added)

Section 5, Warnings and Precautions:
- 5.1 Hemorrhage (updated)
- 5.2 Infections (updated)
- 5.3 Cytopenias (updated)
- 5.5 Second Primary Malignancies (updated)
- 5.6 Tumor Lysis Syndrome (added)
- 5.7 Embryo-Fetal Toxicity (WM added)

Section 6, Adverse Reactions
- 6.1 Clinical Trials Experience: (Format and numbering change)
- 6.2 Postmarketing Experience (added)

Section 8, Use in Specific Populations
- 8.7 Hepatic Impairment (updated)
- 8.9 Plasmapheresis (added)

Section 12, Clinical Pharmacology
- 12.3 Pharmacokinetics
    - Distribution (updated)
    - Elimination (updated)
    - Hepatic Impairment (updated)
    - Drug Interactions: *Coadministration of Ibrutinib with CYP3A Inhibitors* (updated)

Section 16, How Supplied / Storage and Handling (updated)

The following study publications are submitted with the full Prescribing Information.[1] 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) IMBRUVICA® (ibrutinib) capsules [package insert]. Sunnyvale, CA: Pharmacyclics, Inc. Revised 01/2015

2) 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.

3) Wang ML, Hagemeister F, Westin JR, et al. Ibrutinib and rituximab are an efficacious and safe combination in relapsed mantle cell lymphoma: preliminary results from a phase II clinical trial [abstract]. *Blood*. 2014;124(21):627. https://ash.confex.com/ash/2014/webprogram/Paper69685.html

4) Wang ML, Hagemeister F, Westin J, et al. Ibrutinib and rituximab are an efficacious and safe combination in relapsed mantle cell lymphoma: preliminary results from a phase II clinical trial [oral presentation]. 56th Annual Meeting and Exposition of the American Society of Hematology; Dec 6-9, 2014; San Francisco, CA

Sincerely,

Joi Ninomoto, RPh, PharmD
Senior Manager, Medical Information
Pharmacyclics, Inc.