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NCCN Guidelines® Panel: WM/LPL

Dear NCCN:

Pharmacyclics LLC and Janssen Biotech, Inc. co-develop and co-commercialize IMBRUVICA® (ibrutinib). On behalf of Pharmacyclics LLC and Janssen Biotech, Inc., I respectfully request the NCCN Guidelines® - WM/LPL Panel to review the enclosed information of IMBRUVICA (ibrutinib) for the treatment of Waldenström's macroglobulinemia (WM).

Specific Change:

- Recommend ibrutinib + rituximab for Primary Therapy for WM/LPL patients as a Preferred Regimen with Category 1 evidence rating
- Recommend ibrutinib + rituximab for Previously Treated WM/LPL patients as a Preferred Regimen with Category 1 evidence rating

FDA Clearance:
IMBRUVICA® is a kinase inhibitor indicated for the treatment of adult patients with:[1]

- Mantle cell lymphoma (MCL) who have received at least one prior therapy. Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

The use of ibrutinib in combination with rituximab for the treatment of WM is not currently approved by the FDA.

Rationale: **Dimopoulos et al (2018)** recently published[2,3] and presented[4-7] efficacy and safety results from the Phase 3 iNNOVATE study, a randomized trial of ibrutinib + rituximab (i+R) vs. placebo + rituximab (R) in patients with symptomatic treatment-naïve (TN) or relapsed/refractory (R/R) WM (N=150) (PCYC-1127-CA, NCT02165397). With a median follow-up of 26.5 months, the 30-month progression-free survival (PFS) rate was 82% with i+R compared with 28% with R, and the median PFS was not reached vs. 20.3 months (HR 0.20; 95% CI, 0.11-0.38; P <0.001).[2] Higher rates of PFS with i+R vs. R were also observed in relevant prespecified subgroups, including treatment-naïve (HR 0.34; 95% CI, 0.12-0.95) and relapsed patients (HR 0.17; 95% CI, 0.08-0.36), as well as *MYD88*^{L625P}/*CXCR4*^{WT} (HR 0.17; 95% CI, 0.06-0.49), *MYD88*^{L625P}/*CXCR4*^{WHIM} (HR 0.24; 95% CI, 0.09-0.66), and *MYD88*^{WT}/*CXCR4*^{WT} (HR 0.21; 95% CI, 0.04-1.08) genotypes.[2] The 30-month overall survival rate was 94% with i+R vs 92% with R (HR 0.62; 95% CI, 0.17-2.19).[2] Overall and major response rates as assessed by an independent

review committee were significantly higher with i+R vs R (Overall response: 92% vs 47%; Major response: 72% vs 32%; both P<0.001)[2], and major responses were observed with i+R across different *MYD88* and *CXCR4* genotypes (*MYD88*^{L625P}/*CXCR4*^{WT} [78%], *MYD88*^{L625P}/*CXCR4*^{WHIM} [73%], and *MYD88*^{WT}/*CXCR4*^{WT} [64%]).[3]

The most common any grade adverse events (≥20%) occurring in patients on i+R included infusion-related reactions, diarrhea, arthralgia, and nausea. Grade ≥3 adverse events that occurred notably more frequently with i+R vs R included atrial fibrillation (12% vs 1%) and hypertension (13% vs 4%), whereas Grade ≥3 infusion-related reactions (1% vs 16%) and any grade IgM flare (8% vs 47%) occurred less frequently with i+R vs R. Major hemorrhage occurred in 3 patients (4%) in each arm, and the rates of treatment discontinuation due to adverse events were similar with i+R vs. R (5% vs 4%).[2]

In addition, longer term follow-up of studies of single-agent ibrutinib in TN and R/R WM patients have recently been presented at the 23rd European Hematology Association (EHA) Congress.

- **Treon et al (2018)[8]** reported updated follow-up of efficacy and safety from a phase 2, open-label, single-arm study of single-agent ibrutinib in patients with TN WM (N=30) (NCT02604511).
- **Treon et al (2018)[9]** reported updated results, with median time on therapy of 47 months, from a phase 2, open-label, multicenter study of single-agent ibrutinib in patients with R/R WM (N=63) (PCYC-1118E, NCT01614821).

The following references are submitted with the full prescribing information[1] in support of the proposed change. We would like to acknowledge the contributions of the NCCN panel members who are also co-authors or co-contributors of these publications.

1. IMBRUVICA® (ibrutinib) [prescribing information]. Sunnyvale, CA: Pharmacyclics LLC; 2018.
2. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia. *The New England Journal of Medicine.* 2018.
3. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia [supplementary appendix]. *The New England Journal of Medicine.* 2018.
4. Dimopoulos MA, Tedeschi A, Trotman J, et al. Randomized phase 3 trial of ibrutinib/rituximab vs rituximab in Waldenström Macroglobulinemia [abstract]. *Journal of Clinical Oncology.* 2018:Abstract 8003. https://meetinglibrary.asco.org/record/161503/abstract
5. Dimopoulos M, Tedeschi A, Trotman J, et al. Randomized phase 3 trial of ibrutinib/rituximab vs rituximab in Waldenström Macroglobulinemia [oral presentation]. 54th Annual Meeting of the American Society of Clinical Oncology; June 1-5, 2018; Chicago, IL. Abstract 8003.
6. Dimopoulos M, Tedeschi A, Trotman J, et al. MULTINATIONAL, RANDOMIZED PHASE 3 TRIAL OF IBRUTINIB-RITUXIMAB VS PLACEBO-RITUXIMAB IN PATIENTS WITH WALDENSTRÖM'S MACROGLOBULINEMIA [abstract]. *Haematologica.* 2018:Abstract S852. https://learningcenter.ehaweb.org/eha/2018/stockholm/214546/
7. Dimopoulos M. Multinational, randomized phase 3 trial of ibrutinib-rituximab vs placebo-rituximab in patients with Waldenström's macroglobulinemia [oral presentation]. 23rd Congress of the European Hematology Association; 2018; Stockholm, Sweden. Abstract S852.
8. Treon S, Gustine J, Meid K, et al. IBRUTINIB MONOTHERAPY IN SYMPTOMATIC, TREATMENT-NAIVE PATIENTS WITH WALDENSTRÖM'S MACROGLOBULINEMIA [abstract]. *Haematologica.* 2018:Abstract PS1191. https://learningcenter.ehaweb.org/eha/2018/stockholm/215498/
9. Treon S, Meid K, Gustine J, et al. IBRUTINIB SHOWS PROLONGED PROGRESSION-FREE SURVIVAL IN SYMPTOMATIC, PREVIOUSLY TREATED PATIENTS WITH MYD88 MUTATED WALDENSTRÖM'S MACROGLOBULINEMIA: LONG-TERM FOLLOW-UP OF PIVOTAL TRIAL (NCT01614821) [abstract]. *Haematologica.* 2018:Abstract PS1185. https://learningcenter.ehaweb.org/eha/2018/stockholm/215492/

Sincerely,

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Pharmacyclics LLC, an AbbVie Company