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NCCN Guidelines® Panel: Non-Hodgkin's Lymphomas

Dear NCCN,

Pharmacyclics, LLC and Janssen Biotech, Inc. co-develop and co-commercialize IMBRUVICA® (ibrutinib) capsules. On behalf of Pharmacyclics, LLC and Janssen Biotech, Inc., I respectfully request the NCCN Guidelines® - Non-Hodgkin's Lymphomas Panel review the enclosed, updated information for inclusion of the following IMBRUVICA (ibrutinib) combination therapies for the treatment of patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL).

Specific Change:

Recommend IMBRUVICA (ibrutinib) for the treatment of patients with R/R CLL for each of the following treatment options:

- Single-agent therapy: remain listed as Category 1
- Combination therapy with bendamustine and rituximab (BR): addition to currently listed options
- Combination therapy with rituximab: addition to currently listed options

Please consider the following recommendations based upon 2 full publications of ibrutinib in combination with other therapies (Phase 1/2 study PCYC-1108 of ibrutinib and BR,[1] Phase 2 Investigator-sponsored Trial [IST] NCT01520519 or ibrutinib and rituximab[2]) as well as an abstract/oral presentation of the phase 3 study HELIOS (CLL3001) of ibrutinib and BR at the American Society of Clinical Oncology Annual Meeting in 2015.[3,4] Ibrutinib is not currently approved by the U.S. Food and Drug Administration (FDA) for R/R CLL in combination with BR or with rituximab.

FDA Clearance:

The FDA approved IMBRUVICA (ibrutinib) for the treatment of patients with CLL who have received at least one prior therapy, CLL with deletion 17p, mantle cell lymphoma 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), and Waldenström's macroglobulinemia.

A full study report of HELIOS is in preparation and will be submitted to health authorities for future labeling considerations.[5]

Rationale:

***Data in combination therapy*:**

- Ibrutinib plus BR in patients with R/R CLL/small lymphocytic lympohoma (SLL)[1,4]
- Ibrutinib plus rituximab in patients with high-risk CLL/SLL[2]

Interim analysis from a randomized, double-blind, phase 3 study (CLL3001, N=578) evaluating the safety and efficacy of ibrutinib 420 mg orally (PO) once daily (QD) in combination with BR (i+BR) vs placebo plus BR (plb+BR) in patients with previously treated CLL/SLL demonstrated a significantly longer progression-free survival (PFS; primary endpoint) with i+BR (median not reached vs 13.3 months; hazard ratio [HR]: 0.203, 95% confidence interval [CI]: 0.150-0.276, P<0.0001; median follow-up 17.2 months) as assessed by independent review committee. ORR and complete response (CR)/CR with incomplete blood count recovery (CRi) rates were 82.7% vs 67.8% (P<0.0001) and 10.4% vs 2.8% in the i+BR and plb+BR arms, respectively. Median overall survival (OS) was not reached. Incidence of adverse events (AEs) was similar in both

arms. The most common all-grade AEs with i+BR and plb+BR were neutropenia (58% vs 55%) and nausea (37% vs 35%); most common grade 3/4 AEs were neutropenia (54% vs 51%) and thrombocytopenia (15% each arm).[4]

Final results were reported from a primary study and extended follow-up (median treatment durations 15.7 and 35.4 months, respectively) from a multi-center, open-label, phase 1b study (PCYC-1108, N=30) evaluating the safety and efficacy of ibrutinib 420 mg PO QD in combination with BR in patients with R/R CLL/SLL. In the primary study, ORR (secondary endpoint) was 93.3% (CR: 16.7%, nodal PR [nPR]: 10%, PR: 66.7%) and was 93.3% (CR: 40%, nPR: 7%, PR: 47%) in extended follow-up. Responses were reported independent of high-risk clinical or genomic features. The 12-month PFS rate was 85.9% in the primary study, and the estimated 18-, 24-, and 36-month PFS was 78.6%, 78.6%, and 70.3%, respectively, with extended follow-up. The most frequently reported treatment-emergent AEs (≥35%) were diarrhea (70%), nausea (66.7%), fatigue (46.7%), neutropenia (40%), and upper respiratory tract infection (36.7%). The most frequent treatment-emergent grade ≥3 AEs (≥5%) were neutropenia (40%), rash and fatigue (10% each), and thrombocytopenia, febrile neutropenia, and cellulitis (6.7% each). During the study, grade 3 (n=2) and grade 4 (n=2) prolonged hematologic toxicities (primary endpoint) were reported; none discontinued treatment as a result of these toxicities.[1]

Final results were reported from an open-label, single-center, phase 2 study (N=40), which evaluated the safety and efficacy of ibrutinib 420 mg PO QD in combination with rituximab in patients with high-risk CLL/SLL (treated/untreated CLL with deletion 17p or TP53 mutation, or short PFS <36 months after frontline chemo-immunotherapy, or relapsed CLL with deletion 11q). At a median follow-up of 16.8 months, 39 patients were evaluable; ORR was 95% (PR: 34 patients [87%], CR: 3 patients [8%]). One patient with CR was minimal residual disease negative. At 18 months, the PFS (primary endpoint) was 78% (95% CI, 60.6-88.5) and the OS was 83.8% (95% CI, 67.2-92.4). Grade ≥3 toxicities related to therapy included lung infection (5%), neutropenia (6%), and peripheral neuropathy, mucositis, transaminase increase, upper respiratory infection, subdural hematoma, and sepsis (3% each). Respiratory infections were the most common adverse events. Nine patients discontinued therapy, including 3 due to infection, 2 due to progressive disease, and 1 due to Richter's transformation. Of the patients who discontinued, 2 died during the study and 6 died after study discontinuation.[2]

The following study publications are submitted with the full Prescribing Information.[6] 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. Brown JR, Barrientos JC, Barr PM, et al. The Bruton tyrosine kinase inhibitor ibrutinib with chemoimmunotherapy in patients with chronic lymphocytic leukemia. *Blood.* 2015;125(19):2915-2922.
2. Burger JA, Keating MJ, Wierda WG, et al. Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: A single-arm, phase 2 study. *Lancet Oncol.* 2014;15(10):1090-1099.
3. Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab (BR) in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): First results from a randomized, double-blind, placebo-controlled, phase III study [oral presentation]. American Society of Clinical Oncology Annual Meeting; May 29-June 2, 2015; Chicago, IL. Abstract LBA7005.
4. Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab (BR) in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): First results from a randomized, double-blind, placebo-controlled, phase III study [abstract]. *J Clin Oncol.*2015;33(5s):LBA7005.
5. Independent data monitoring committee unanimously recommends unblinding of Imbruvica® (ibrutinib) phase III combination HELIOS trial based on interim analysis showing significant improvement in progression-free survival in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma [press release]. Sunnyvale, CA: Pharmacyclics, LLC; March 16, 2015. http://www.prnewswire.com/news-releases/independent-data-monitoring-committee-unanimously-recommends-unblinding-of-imbruvica-ibrutinib-phase-iii-combination-helios-trial-based-on-interim-analysis-showing-significant-improvement-in-progression-free-survival-in-patient-300051103.html. Accessed May 14, 2015.
6. Pharmacylics, LLC. Sunnyvale, CA. IMBRUVICA® (ibrutinib) capsules [package insert].

Sincerely,

Andrea Lo-Rossi, PhD
Scientific Communications, Manager
Pharmacyclics, LLC