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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 information of IMBRUVICA (ibrutinib) for induction therapy of patients with mantle cell lymphoma (MCL).

Specific Change: Recommend ibrutinib in combination with Rituxan® (rituximab) for induction therapy as a component of aggressive therapy with shortened hyper-cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) alternating with rituximab plus high-dose methotrexate-cytarabine for MCL as a category 2A rating.

FDA Clearance:

IMBRUVICA® is a kinase inhibitor indicated for the treatment of patients with:

- 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 of clinical benefit in confirmatory trials.
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL).
- Chronic lymphocytic leukemia/Small lymphocytic lymphoma (SLL) with 17p deletion.
- Waldenström's macroglobulinemia (WM).

Ibrutinib is not currently approved by the FDA for patients with previously untreated MCL.

Rationale: Wang, et al. recently presented interim results of a phase 2 study of induction therapy with ibrutinib in combination with rituximab followed by shortened chemoimmunotherapy consolidation, hyper-CVAD alternating with rituximab, methotrexate, and cytarabine, in young (≤65 yo) and fit patients with newly diagnosed and untreated MCL (N=50).[2,3] In evaluable patients (n=45), overall response rate (ORR) to ibrutinib plus rituximab was 100% (27% partial response [PR], 73% complete response [CR]).[2] Of the patients (n=19) who completed therapy with ibrutinib plus rituximab followed by chemoimmunotherapy consolidation, the ORR was 100%, all of which were CRs.[3] After median follow-up of 9 months, median duration of response (DOR), progression-free survival (PFS), and overall survival (OS) had not yet been reached.[2]

Hematologic toxicity (occurring in ≥20%) was anemia and non-hematologic toxicities (≥20%) were fatigue, diarrhea, myalgia, mucositis oral, dizziness, peripheral sensory neuropathy, skin disorder, nausea, dyspnea, constipation, dry eye, blurred vision, edema, and hyperglycemia with ibrutinib plus rituximab. With patients who also completed shortened consolidation therapy, non-hematologic toxicities (≥20%) were fatigue, nausea, peripheral sensory neuropathy, and constipation.[2]

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) capsules [prescribing information]. Sunnyvale, CA: Pharmacyclics LLC. Revised 06/2016.
2. Wang ML, Lee H, Thirumurthi S, et al. Chemotherapy-free induction with ibrutinib-rituximab followed by shortened cycles of chemo-immunotherapy consolidation in young, newly diagnosed mantle cell lymphoma patients: a phase II clinical trial [oral presentation]. 58th Annual Meeting & Exposition of the American Society of Hematology. Dec 3-6, 2016; San Diego, CA. Abstract 147.
3. Wang ML, Lee H, Thirumurthi S, et al. Chemotherapy-free induction with ibrutinib-rituximab followed by shortened cycles of chemo-immunotherapy consolidation in young, newly diagnosed mantle cell lymphoma patients: a phase II clinical trial [abstract]. Blood. 2016;128 (22):Abstract 147.

Sincerely,

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