December 19, 2019

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Date of request: December 19, 2019
NCCN Guidelines® Panel: B-Cell Lymphomas

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® - B-Cell Lymphomas Panel to review the enclosed information regarding IMBRUVICA (ibrutinib) for the treatment of mantle cell lymphoma (MCL).

Specific Change: Please find below proposed changes for the committee's consideration.

Indication		Proposed Changes
MCL Second-Line Therapy	Short response duration to prior chemoimmunotherapy (< expected median PFS)	• Ibrutinib ± rituximab: Retain as preferred regimen
	Extended response duration to prior chemoimmunotherapy (> expected median PFS)	• Ibrutinib ± rituximab: Recommend as preferred regimen, based upon updated Rule, et al (ASH 2019) analysis described in the *Rationale* section below.

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

Rationale:
An updated pooled-analysis (up to 7.5 years of extended follow-up) of 370 patients with R/R MCL treated with ibrutinib across 3 studies (Phase 2 PCYC-1104, Phase 2 SPARK, and Phase 3 RAY) was recently presented at ASH 2019 by **Rule, et al**. In this updated analysis, outcomes with 2L ibrutinib according to frontline progression of disease (POD) status were assessed: POD24 (progressed within 24 months) or POD≥24 (progressed after ≥24 months).

A total of 99 of the 370 patients received ibrutinib as 2L therapy. Of these patients, 43% had POD24 and 57% had POD≥24. Regardless of the duration of frontline POD, median PFS with 2L ibrutinib was as long or longer than median estimated PFS in frontline therapy.

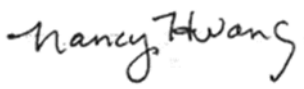
- POD24: median PFS with 2L ibrutinib was similar to median estimated PFS in frontline (13.8 vs 14 mos).
- POD≥24: median PFS with 2L ibrutinib was 15.3 months longer than median estimated PFS in frontline (57.5 vs 42.2 mos).

In the overall population, median PFS on ibrutinib was 12.5 mos compared with a median estimated PFS on the prior regimen of 10.9 mos. Half of patients experienced a longer PFS with ibrutinib than with the prior regimen, and 27% of patients achieved ≥1 incremental year of PFS benefit with ibrutinib (i.e., PFS with ibrutinib was ≥1 year longer than estimated PFS with the prior regimen).

The following reference is submitted with the full prescribing information[1] for your reference. We would like to acknowledge the contributions of the NCCN panel members who are also co-authors or co-contributors of this publication.

1. IMBRUVICA® (ibrutinib) [prescribing information]. Sunnyvale, CA: Pharmacyclics LLC; 2018.
2. Rule S, Dreyling M, Goy A, et al. Long-Term Outcomes With Ibrutinib Versus the Prior Regimen: a Pooled Analysis in Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL) With up to 7.5 Years of Extended Follow-up [poster presentation]. 61st Annual Meeting and Exposition of the American Society of Hematology; December 7-10, 2019; Orlando, FL, USA. Abstract 1538.

Sincerely,



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