On behalf of Bayer Healthcare Pharmaceuticals, I respectfully request the NCCN® (Non-Hodgkin’s lymphoma panel) to review the enclosed data for compendium listing of Aliqopa® (copanlisib) in the NCCN Clinical Practice Guidelines in Oncology™.

Specific Changes: Compendium listing of Aliqopa® (copanlisib) as therapy for adult patients with relapsed or refractory Marginal Zone lymphoma (MZL) based on the results of the phase II open label (CHRONOS-1) trial.

FDA Clearance: On September 14, 2017 the U.S. Food and Drug Administration (FDA) approved copanlisib under the brand name of Aliqopa® for the treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies. Accelerated approval was granted for this indication based on the overall response rate. Subsequently, The NCCN® (Non-Hodgkin’s lymphoma panel) listed copanlisib as indicated for second-line and subsequent therapy.

I am providing additional data for consideration of including compendium listing of copanlisib in your guidelines for relapsed and/or refractory Marginal Zone Lymphoma. We believe that these data are comparable to those of idelalisib, an oral δPI3K inhibitor which is already included in the NCCN guidelines.

Copanlisib Mechanism of Action: Copanlisib is a phosphatidylinositol-3-kinase (PI3K) inhibitor that targets all four of the class I PI3K isoforms that contribute to sustained PI3K pathway activation, with predominant inhibitory activity against both PI3Kα and PI3Kδ. Preclinically, copanlisib has been shown to inhibit both PI3Kα and PI3Kδ isoforms at sub-nanomolar concentrations. Dysregulation of the PI3K pathway plays an important role in NHL.

Rationale: In a single-arm, multicenter phase II (CHRONOS-1) trial copanlisib has shown activity in patients with Marginal Zone B-cell non-Hodgkin lymphoma who had relapsed disease following at least two prior systemic treatments. Study results of this trial were presented at the American Association for Cancer Research (AACR) in April 2017 and epublished in JCO on October 4th, 2017.

In this global, single-arm, multicenter phase II (CHRONOS-1) trial 142 patients with relapsed or refractory indolent NHL were treated with 60 mg copanlisib as a 1-hour intravenous (IV) infusion on Days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on/one week...
Treatment continued until disease progression or unacceptable toxicity. The study primary endpoint was overall response rate (ORR). The full analysis set comprised 142 patients with indolent B-cell Lymphoma, of whom 23 patients had Marginal Zone Lymphoma (MZL).

The trial results for the Marginal Zone Lymphoma patients are summarized below with subset analysis comprised 23 MZL patients (15 nodal, 4 splenic and 4 MALT lymphomas):

- Copanlisib demonstrated promising anti-tumor efficacy in a heavily pretreated patient population with Marginal Zone Lymphoma:
  - The ORR was 70% (complete response rate 13%) with ORR of 80% in patients with nodal disease (twelve of fifteen patients).
  - Median duration of response (DOR) had not been reached (range 1-728 days) with 85% estimated to be in response at 9 months.

- There were low rates of severe elevation of hepatic transaminases, diarrhea or pneumonitis.
  - The most common AEs were infusion-related hyperglycemia and hypertension, which were transient and mostly self-limiting.
  - Serious AEs including pneumonitis (1.4% [2/142], grade 3) and colitis (0.7% [1/142], grade 4).
  - Rates of opportunistic or fatal infections or other fatal TEAEs were low. In the MZL subset, there were no non-fatal opportunistic infections and no deaths attributed to copanlisib.
    - Serious pneumocystis jiroveci pneumonia (PJP) occurred in 0.6% of 317 (pool of patients with hematologic and solid tumors) patients treated with copanlisib.

Enclosed is the approved Packaging Insert (Pl). Please note that there are no black box warnings.

I appreciate your review and consideration of this recommendation. Should you have any questions regarding the content of this letter, please do not hesitate to contact me.

Sincerely,

Joseph Germino, MD, PhD
Vice President US Medical Affairs Specialized Therapeutics
Bayer Healthcare Pharmaceuticals
100 Bayer Boulevard, P.O. Box 915
Whippany, NJ 07981
(862) 404-5184
Reference List

1. Aliqopa®US Prescribing Information
2. Martin Dreyling et al. “Copanlisib in patients with relapsed or refractory indolent B-cell lymphoma: primary results of the pivotal CHRONOS-1 study” AACR Annual Meeting, April 1-5, 2017, Washington DC, USA
3. Martin Dreyling et al. Copanlisib in patients with relapsed or refractory follicular lymphoma” Poster presented at the 2017 ASCO Annual Meeting, June 2-6, 2017, Chicago, IL, USA
5. Martin Dreyling et al.“Efficacy of copanlisib monotherapy in patients with relapsed or refractory marginal zone lymphoma: Subset analysis from the CHRONOS-1 trial. Abstract accepted for ASH Annual Meeting, December 9-12, 2017. Atlanta, GA, USA