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Date of request: September 15, 2017
NCCN Guidelines Panel: Non-Hodgkin's Lymphomas Panel

On behalf of Bayer HealthCare Pharmaceuticals, I respectfully request the NCCN[®] (*Non-Hodgkin's Lymphomas Panel*) to review the enclosed data for inclusion of Aliqopa[®] (copanlisib) in the NCCN Clinical Practice Guidelines in Oncology[™].

Specific Changes: Aliqopa[®] (copanlisib) as therapy for adult patients with relapsed or refractory indolent Non-Hodgkin's Lymphoma (Follicular Lymphoma) 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 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.

I am providing these data for consideration of including copanlisib in your guidelines for relapsed follicular lymphoma. We believe that these data are comparable to those of idelalisib, an oral δ PI3K 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 PI3K α and PI3K δ . Preclinically, copanlisib has been shown to inhibit both PI3K δ and PI3K α 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 follicular B-cell non-Hodgkin lymphoma who had relapsed disease following at least two prior systemic treatments. Study results from this trial were presented at the American Association for Cancer Research (AACR) in April 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 off). Treatment continued until disease progression or unacceptable toxicity. The study primary end point was overall response rate (ORR). The full analysis set comprised 142 patients, of whom 141 patients had indolent lymphoma, including 23 patients with Marginal Zone Lymphoma (MZL).



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The trial results are summarized below:

- Copanlisib demonstrated promising anti-tumor efficacy in a heavily pretreated patient population with indolent B-cell lymphoma (including multiple subtypes)
 - The ORR was 59% (complete response rate 12%)
 - Median duration of response (DoR) was 22.6 months; median PFS was 11.2 months
 - In the subset of follicular lymphoma patients (n=104) the ORR was 59% with 14% CR (median DoR 12.2 months, median PFS 11.2 months)

- There were low rates of severe elevation of hepatic transaminases, diarrhea, or pneumonitis
 - The most common AEs were hyperglycemia and hypertension, which were transient and mostly self-limiting
 - Serious AEs included 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
 - Serious pneumocystis jiroveci pneumonia (PJP) occurred in 0.6% of 317 (pool of patients with hematologic and solid tumors) patients treated with copanlisib monotherapy

Enclosed is the approved Packaging Insert (PI). 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,

A handwritten signature in black ink that reads "Joseph Germino".

Joseph Germino, MD, PhD
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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