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NCCN Guidelines Panel: Non-Hodgkin's Lymphomas Panel

On behalf of Bayer HealthCare Pharmaceuticals, I thank the NCCN[®] (*Non-Hodgkin's lymphoma panel*) for inclusion of copanlisib (Aliqopa[®]) in the NCCN Clinical Practice Guidelines in Oncology[™]. Review of the NCCN Guidelines For Patients[®] (Non-Hodgkin's Lymphoma) under "*Overview of cancer treatments*" and "*Copanlisib*", reference is made to copanlisib causing serious but uncommon side effects such as liver problems. I respectfully request the NCCN to consider to modify this as serious liver problems were not seen with copanlisib monotherapy in patients with NHL.

Furthermore, I respectfully request the NCCN to consider to modify the indication for copanlisib from stating: copanlisib (refractory to at least two prior therapies) to state: copanlisib (relapse after two prior systemic therapies). This would be consistent with the FDA label indication. The manuscript is now available in J Clin Oncol [Epub ahead of print] Oct 4, 2017 (*Dreyling M, Santoro A, Mollica L et al: Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma*) for consideration as a reference.

In view of the discussion section being updated in the NCCN Guidelines for B-cell lymphomas, consider including the following information in regards to copanlisib (since no information referenced to copanlisib is in the current version of the Follicular Lymphoma discussion section).

Discussion: 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 δ and PI3K α isoforms at sub-nanomolar concentrations. Copanlisib demonstrated promising clinical activity in phase I study in patients with relapsed/refractory Follicular Lymphoma⁵. The safety and efficacy of copanlisib in patients with relapsed indolent NHL following at least two prior systemic treatments was evaluated in a single-arm, multicenter phase II (CHRONOS-1). In this study, 141 patients with relapsed or refractory indolent NHL (104 patients with FL, 23 patients with MZL, 8 patients with SLL and 6 patients with LPL/WM) with prior rituximab and an alkylating agent therapy were treated with copanlisib 60 mg as a 1-hour intravenous (IV) infusion on Days 1, 8 and 15 of a 28-day treatment cycle on an intermittent schedule (3 weeks on/one week off) until disease progression or unacceptable toxicity. Majority of the patients (80%) had stage III or IV disease and 26% of FL patients had grade 3a histology. Among patients with FL, median prior lines of therapy was 3 (2-8) with 62% of patients refractory to last regimen with 41% refractory to last combination of anti-20 immunotherapy and alkylating agent. The primary end point of the study was the ORR. The median duration of treatment with copanlisib was 22 weeks. Copanlisib demonstrated promising anti-tumor efficacy in a heavily pretreated patient population with indolent NHL with ORR of 59% (12% CR and 47% PR) with

median duration of response (DoR) of 22.6 months and median PFS of 11.2 months with median duration of OS not reached yet. In the subset of FL patients (n=104), the ORR was 59% (14% CR and 45% PR) with disease control rate of 88%, median DoR 12.2 months and median PFS of 11.2 months. The median duration of safety follow up was 24 weeks. The most common treatment-emergent adverse events of grade 3 and grade 4 were infusion-related hyperglycemia (34%,7%) and infusion-related hypertension (24%,none) which were transient and mostly self-limiting, neutropenia (8%,16%) and lung infection (13%,2%) with low rates of grade 3 or grade 4 elevations of hepatic transaminases (1%,1%) or diarrhea (5%, none). Serious adverse events included pneumonitis (1.4%, grade 3), colitis (0.7%, grade 4) 3 non-fatal opportunistic infections (2 *Pneumocystis jiroveci* pneumonia; 1 bronchopulmonary aspergillosis infection), or fatal infections or other fatal treatment-emergent adverse events were low in patients treated with copanlisib.

Based on the results of this study, copanlisib (60 mg IV on Days 1,8, 15 on a 28-day cycle) was recently approved by the FDA for the treatment of relapsed FL in patients who have received at least two prior systemic therapies. The NCCN Guidelines have included copanlisib as an option for FL patients with relapsed patients in need of subsequent therapy.

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

Sincerely,



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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
4. Dreyling M, Santoro A, Mollica L et al: Phosphatidylinositol 3-Kinase Inhibition by Copanlisib in Relapsed or Refractory Indolent Lymphoma. J Clin Oncol [Epub ahead of print] Oct 4, 2017

5. Patnaik A, Appleman LJ, Tolcher AW et al: First-in-human phase I study of copanlisib (BAY 80-6946), an intravenous pan-class I phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors and non-Hodgkin's lymphomas. *Ann Oncol* 27:1928-1940, 2016