

A Closer Look at Copanlisib



Martin Dreyling, MD
Professor of Medicine
Department of Medicine III
University Hospital, LMU Munich
Munich, Germany

Copanlisib (Aliqopa, Bayer HealthCare) received accelerated approval on September 14, 2017, for the treatment of adults with relapsed follicular lymphoma who have received at least 2 prior systemic therapies. Copanlisib is an inhibitor of phosphoinositide 3-kinase.

H&O When did you first start using copanlisib on an investigational basis?

MD A couple of years ago, we published the results of our laboratory work on the effects of this compound in the journal *Drugs*. The laboratory work showed us that combined inhibition of PI3K- α and PI3K- δ is the most powerful approach to treatment with phosphoinositide 3-kinase (PI3K) isoforms. Copanlisib is also an inhibitor of mammalian target of rapamycin (mTOR), which may contribute to its efficacy.

On the basis of these highly encouraging in vitro data, we began the first phase 2 study with copanlisib 2 years ago. This early trial included patients with a variety of lymphoma subtypes. For example, one of my patients was 79-year-old man with relapsed mantle cell lymphoma and multiple comorbidities. Although his disease was quite advanced and he had a pleural effusion, he tolerated copanlisib very well. His response was excellent—a very good partial response that was close to a complete response. This experience convinced me that copanlisib would become an important addition to our current therapeutic armamentarium.

H&O Could you talk about CHRONOS-1, which served as the basis for approval of the drug?

MD CHRONOS-1 (Open-Label, Uncontrolled Phase II Trial of Intravenous PI3K Inhibitor BAY80-6946 in

Patients With Relapsed, Indolent or Aggressive Non-Hodgkin's Lymphomas) was a large international phase 2 study of 142 patients that was undertaken on the basis of the early results of the first phase 2 study. All patients received a 1-hour infusion containing 60 mg of copanlisib on days 1, 8, and 15 of a 28-day cycle.

The study protocol required patients to have received at least 2 prior treatments, which meant that all the patients had received rituximab (Rituxan, Genentech/Biogen Idec) and alkylating agents. Approximately 60% of the lymphoma had been refractory to the last regimen. It is especially challenging when disease is refractory to our most effective compounds.

One of the notable characteristics of copanlisib is that it is administered intravenously. I initially thought that this route of administration—weekly infusions 3 times during a 4-week cycle—would be a disadvantage of copanlisib, but it ended up being a major advantage. In fact, the most frequent side effects of copanlisib—hypertension and hyperglycemia—were only temporary and easily managed. A side effect of special interest was colitis, which is a major problem with the δ -specific PI3K inhibitor idelalisib (Zydelig, Gilead), but colitis was observed in only 1 of the 142 patients taking copanlisib. In general, the rate of gastrointestinal side effects was low, with only 4% of patients experiencing grade 3 diarrhea. Furthermore, grade 3 or 4 pneumonitis occurred in only 1.4% of the study patients, a rate significantly lower than what is seen with idelalisib.

During this study, 3 deaths occurred that were considered treatment-related. Death was due to lung infection in 1 case (which is not surprising because we are talking about an older patient population—the oldest patient was 82 years old), respiratory failure in 1 case, and a thromboembolic event in 1 case, which may or may not have been related to copanlisib.

The response to treatment, as defined by the Lugano criteria, was quite striking. The overall response rate was 59%, with a median duration of response of 22.6 months.

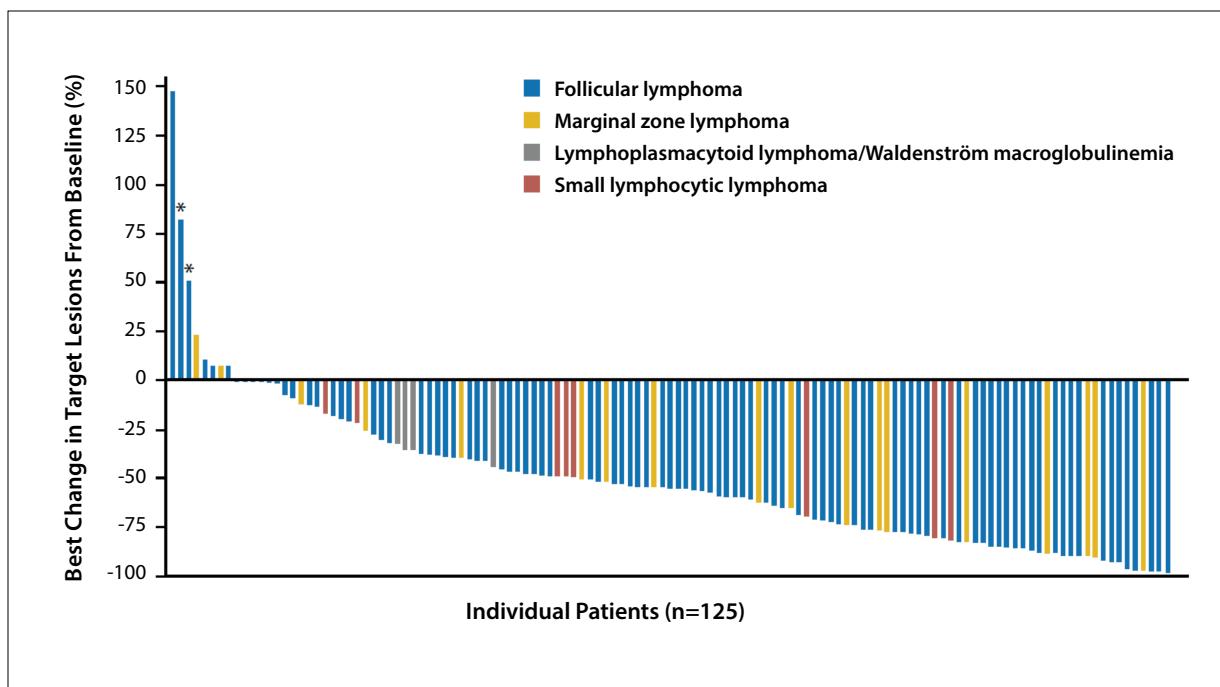


Figure. Best response in target lesions. The percentage best change in the sum of the diameters of all target lesions from baseline as assessed by the investigator is shown. Of the 142 patients included in the full analysis set, the percentage best change in target lesions for the investigator's on-site assessment could not be determined in 15 (11%). In addition, for 1 patient who had follicular lymphoma (with a best response of partial response), the percentage best change in target lesions was not calculated. For 1 patient who was classified by the investigator as having follicular lymphoma but who was reclassified by independent assessment as having diffuse large B-cell lymphoma, the percentage change in lesions (increase of 250%) is not shown (*). The patient was assessed by independent review as having stable disease.

From Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma [published online October 4, 2017]. *J Clin Oncol*. doi:10.1200/JCO.2017.75.4648. Republished with permission.

As seen in the waterfall plot (Figure), at least some response occurred in nearly all the patients. The objective response rate was 59% for patients with follicular lymphoma and 70% for patients with marginal zone lymphoma. When we did gene expression profiling, we found that patients with indolent lymphoma or follicular lymphoma were more likely to respond to copanlisib if they had high level of gene expression of PI3K and B-cell receptor (BCR) pathway signaling components.

H&O Do you have any pointers for physicians when it comes to managing the side effects of copanlisib?

MD If they have limited experience managing general internal medicine complications, such as hyperglycemia and hypertension, I recommend that they join forces with internal medicine specialists. However, these problems are usually temporary, and we do not expect any type of long-term toxicity.

H&O What kind of future do you foresee for the use of copanlisib in trials and in the real world?

MD Although copanlisib is currently approved for use only in third-line treatment and as monotherapy, trials are now examining its use earlier in treatment and in combination with other agents, such as rituximab (NCT02367040) and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or bendamustine/rituximab (NCT02626455).

These studies will be crucial to illuminate the best combination with copanlisib in the therapeutic algorithm for indolent lymphoma. I suspect that earlier approaches will be more effective, and so far, we do not have any discouraging signals concerning safety. The German Lymphoma Alliance (GLA) is trying to initiate a trial of copanlisib in combination with an anti-CD20 antibody in first-line therapy.

H&O Could you talk a bit more about the use of copanlisib to treat conditions other than follicular lymphoma?

MD I would not use copanlisib in chronic lymphocytic leukemia because several effective treatments are already available, including Bruton tyrosine kinase (BTK) inhibitors and B-cell lymphoma 2 (BCL-2) inhibitors. I would also avoid the use of copanlisib in Waldenström macroglobulinemia because its activity seems to be limited. In addition to follicular lymphoma, the obvious disease in which we should consider the use of copanlisib is marginal zone lymphoma. The previous trial also showed some nice responses to copanlisib among patients with mantle cell lymphoma. Therefore, I think copanlisib should also be explored in mantle cell lymphoma, potentially in some new combinations.

Finally, we have seen some cases—and this has been confirmed by in vitro experiments—in which copanlisib seems to have efficacy in aggressive lymphoma, including both diffuse large B-cell lymphoma and T-cell lymphoma. Finding new treatments for T-cell lymphoma is especially important because this is a disease for which we do not have any effective salvage treatments.

For now, I recommend that outside clinical trials, oncologists use copanlisib as specified in its approval—as third-line treatment for patients with follicular lymphoma.

H&O What else should oncologists who use copanlisib know about the drug?

MD The trials that have been conducted thus far have used a continuous schedule until progression. Given that many of these patients have indolent lymphoma, I think that we need to test ways to make the schedule more user-friendly. For example, a schedule that is currently being tested involves a standard induction over 6 months followed by maintenance treatment with 1 dose every 4 weeks. Although it is too early to recommend such a schedule, it may be an optimized approach that we will see used in the future.

H&O Is there anything else that you would like to add?

MD It is critical that we retest copanlisib and other registered compounds in a real-life setting. Are these agents really holding up to their promise when it comes to both toxicity and effectiveness? Although we have a much longer follow-up for copanlisib than we did for prior PI3K inhibitors at the time of approval, we still do not know what will happen after 3 to 5 years—we must keep our eyes open.

Disclosure

Dr Dreyling has served as an advisor for Bayer HealthCare, Celgene, and Janssen; received research grants from Celgene, Janssen, Mundipharma International, Pfizer, and Roche; and received honoraria from Celgene, Janssen, Gilead Sciences, Mundipharma International, Pfizer, and Roche.

Suggested Readings

ClinicalTrials.gov. Copanlisib and rituximab in relapsed indolent B-cell non-Hodgkin's lymphoma (iNHL). <https://clinicaltrials.gov/ct2/show/NCT02367040>. Accessed November 27, 2017. Identifier: NCT02367040.

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