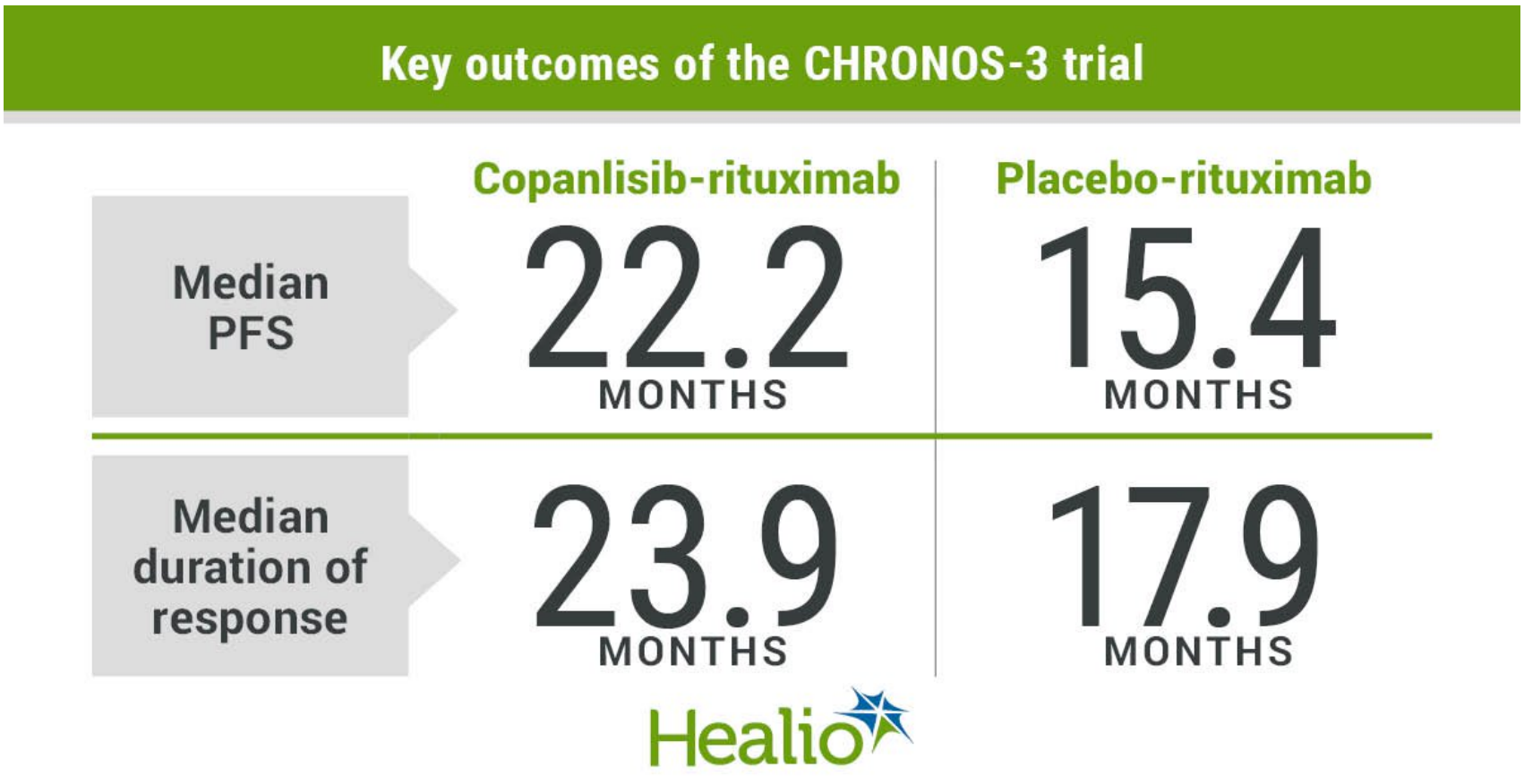
June 07, 2021 3 min read

# Copanlisib regimen improves outcomes in pretreated follicular, marginal zone lymphoma

The addition of copanlisib to rituximab extended PFS among patients with relapsed follicular lymphoma or marginal zone lymphoma, according to a subset analysis of the randomized phase 3 CHRONOS-3 trial.

The findings — presented during the virtual ASCO Annual Meeting — showed the combination appeared associated with a higher objective response rate and more durable responses than placebo and rituximab (Rituxan; Genentech, Biogen). The regimen also exhibited a manageable safety profile.




Data derived from Matasar MJ, et al. Abstract 7510. Presented at: ASCO Annual Meeting (virtual meeting); June 4-8, 2021.

"Copanlisib is the first PI3 kinase inhibitor to be safely combined with rituximab in a randomized phase 3 setting, and the first to demonstrate broad and superior efficacy in combination with rituximab [for] patients with relapsed follicular lymphoma or marginal zone lymphoma," **Matthew J. Matasar, MD,** medical oncologist and lymphoma specialist at Memorial Sloan Kettering Cancer Center, said during a presentation. "[This represents] a potential new treatment option [for] this population."

Rituximab monotherapy is approved for patients with relapsed, indolent non-Hodgkin lymphoma who experience an extended progression-free and treatment-free interval after previous rituximab-based therapy and are either unfit or unwilling to receive chemotherapy.

**Matthew J. Matasar**

Copanlisib (Aliqopa, Bayer), a PI3 kinase inhibitor, received FDA approval in 2017 as monotherapy for adults with relapsed follicular lymphoma who received at least two prior systemic therapies.

The double-blind CHRONOS-3 study compared the copanlisib-rituximab combination with placebo-rituximab for patients with relapsed indolent NHL who relapsed after least one prior line of rituximab-containing therapy. Most patients had follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia.

All patients had been progression- and treatment-free for at least 12 months after prior rituximab-based therapy, or for at least 6 months if they were unwilling or unfit to receive chemotherapy.

Researchers randomly assigned patients 2:1 to copanlisib (60 mg via IV on days 1,8 and 15 of 28-day cycles) with rituximab (375 mg/m$^2$ via IV on days 1, 8, 15 and 22 of cycle 1, then day 1 of cycles 3, 5, 7 and 9) or placebo-rituximab.

Centrally assessed PFS by Cheson 2014 criteria served as the primary endpoint. Secondary endpoints included ORR, duration of response, complete response rate, time to progression and treatment-emergent adverse events.

Investigators assessed all randomly assigned patients for efficacy; safety assessments included patients who received at least one copanlisib/placebo or rituximab dose.

Data cutoff was Aug. 31, 2020.

The study met its primary endpoint. As Healio previously reported, initial results showed the copanlisib-rituximab regimen reduced risk for disease progression or death by 48%.

During ASCO, Matasar reported results of a preplanned subset analysis of 370 patients (median age, 62 years; range, 28-91) with relapsed follicular lymphoma or marginal zone lymphoma. Researchers assigned 250 patients (follicular lymphoma, n = 184; marginal zone lymphoma, n = 66) to copanlisib-rituximab. The other 120 (follicular lymphoma, n = 91; marginal zone lymphoma, n = 29) received placebo-rituximab.

Treatment groups were balanced with regard to sex (male, 46% for copanlisib-rituximab vs. 51.7% for placebo-rituximab), ECOG performance status (0 or 1, 96.4% vs. 100%), medical history of diabetes (14.8% vs. 13.3%) or hypertension (38% vs. 34.2%), histology (follicular lymphoma, 73.6% vs. 75.8%), median time since last systemic therapy (25.2 months vs. 25.4 months), median time since initial diagnosis (68.1 months vs. 72.6 months), previous lines of therapy (one, 47.2% vs. 46.7%; two, 26% vs. 27.5%; three or more, 26.8% vs. 25.8%) and percentage of patients unwilling or unfit to receive chemotherapy (22.4% vs. 21.7%).

Median follow-up was 18.5 months.

Results showed a statistically significant improvement in PFS in the copanlisib-rituximab group (median, 22.2 months vs. 15.4 months; HR = 0.55; 95% CI, 0.4-0.76).

The combination also appeared superior with regard to median time to progression (27.5 months vs. 15.4 months; HR = 0.5; $P$ = .00001), ORR (82.4% vs. 50.8%), complete response rate (37.6% vs. 18.3%), partial response rate (44.8% vs. 32.5%) and median duration of response (23.9 months vs. 17.9 months).

The safety analysis included 249 patients assigned copanlisib-rituximab and 116 patients assigned placebo-rituximab. The safety profile of the combination appeared consistent with known toxicities of each agent as monotherapy, Matasar said.

The most common treatment-emergent adverse events that occurred more frequently in the copanlisib-rituximab group included hyperglycemia (all grade, 72.7% vs. 23.3%; grade 3 or higher, 59% vs. 7.8%); hypertension (all grade, 53.8% vs. 19.8%; grade 3, 43% vs. 8.6%), diarrhea (all grade, 35.3% vs. 12.1%; grade 3, 5.6% vs. 0%), nausea (all grade, 22.5% vs. 13.8%; grade 3, 0.8% vs. 0.9%), pyrexia (all grade, 21.7% vs. 7.8%; grade 3, 2% vs. 0%), neutropenia (all grade, 19.3% vs. 18.1%; grade 3/grade 4, 15.2% vs. 13.8%) and anemia (all grade, 18.1% vs. 6.9%; grade 3/grade 4, 4.4% vs. 0.9%).

**Read next**

Copanlisib regimen extends PFS in lymphoma subset

FDA grants fast track designation to 'switchable' CAR-T for B-cell malignancies

A higher percentage of patients assigned copanlisib-rituximab developed pneumonitis (all grade, 6.8% vs. 1.7%; grade 3 or higher, 2.8% vs. 0.9%).

## PERSPECTIVE

### Lee Greenberger, PhD

The combination of copanlisib — an IV, intermittently-dosed PI3K inhibitor — with rituximab for relapsed, indolent NHL showed a statistically significant improvement in median PFS compared with rituximab alone. This appears to be a new option to treat relapsed follicular lymphoma, marginal zone lymphoma or Waldenström macroglobulinemia.

The FDA previously approved copanlisib for patients with follicular lymphoma who failed at least two systemic therapies. The combination of copanlisib with rituximab after relapse for patients who already received rituximab is an interesting therapeutic approach. Although such phase 3 combination studies with a comparison arm require a large number of patients and considerable time, they are advancing new treatment options. We can expect additional combination studies, as well as CD19-directed chimeric antigen receptor T-cell therapies, to be integrated into the treatment of indolent NHLs in the future.

**Lee Greenberger, PhD**
The Leukemia & Lymphoma Society

**Disclosures:** Greenberger reports no relevant financial disclosures.

## Read more about

copanlisib rituximab marginal zone lymphoma follicular lymphoma memorial sloan kettering cancer center lymphoma

April 10, 2021 2 min read

# Copanlisib-rituximab combination extends PFS in relapsed indolent non-Hodgkin lymphoma

The addition of copanlisib to rituximab increased response rates and significantly extended PFS among patients with relapsed indolent non-Hodgkin lymphoma, according to study results.