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Copanlisib-Rituximab Combination Cuts Lymphoma Progression or Death by Nearly Half in CHRONOS-3 Trial

PHILADELPHIA – A combination of copanlisib (Aliqopa) and rituximab led to a 48 percent reduction in the risk of disease progression or death compared with placebo and rituximab in patients with relapsed indolent non-Hodgkin lymphoma, according to data from the phase III trial CHRONOS-3, presented during Week 1 of the virtual AACR Annual Meeting 2021, held April 10-15.

"We are glad to see that copanlisib could be safely combined with rituximab for the long-term treatment of patients with relapsed indolent non-Hodgkin lymphoma," said Matthew J. Matasar, MD, associate member of Lymphoma Service at Memorial Sloan Kettering Cancer Center (MSK).

"The CHRONOS-3 trial met its primary endpoint of progression-free survival (PFS), with improved outcomes seen in several subtypes of indolent lymphoma included in the study. To my knowledge, this is the first study to report such a broad benefit in patients with relapsed indolent non-Hodgkin lymphoma," Matasar added.

Rituximab given as monotherapy is a standard of care in patients with relapsed indolent lymphomas of many subtypes, Matasar said. "However, it does not work as frequently, or for as long, as we would like," he added.

Preclincial studies have shown that lymphoma cells rely on a cell-signaling pathway called the PI3K pathway for survival, and activation of PI3K plays a role in the resistance to rituximab, Matasar explained. Copanlisib is a potent PI3K inhibitor approved as monotherapy for patients with follicular lymphoma, a common indolent lymphoma, whose disease has relapsed after at least two courses of prior treatment.

In CHRONOS-3, patients with relapsed indolent non-Hodgkin lymphoma were randomly assigned to copanlisib plus rituximab (307 patients) or to placebo plus rituximab (151 patients). Of them, 60 percent had follicular lymphoma, 20.7 percent had marginal zone lymphoma, 10.9 percent had small lymphocytic lymphoma, and 8.3 percent had lymphoplasmacytic lymphoma/Waldenström macroglobulinemia.

After a median follow-up of 19.2 months, the study met its primary endpoint of PFS with a 48 percent reduction in the risk of lymphoma progression or death in the copanlisib-rituximab arm. Significant reductions were seen for follicular lymphoma, marginal zone lymphoma, and small lymphocytic lymphoma. Median PFS was 21.5 months in the copanlisib-rituximab arm and 13.8 months in the placebo-rituximab arm.

Overall response rate was 80 percent in the copanlisib-rituximab arm, versus 47.7 percent in the placebo-rituximab arm. Complete response rate was 33.9 percent in the copanlisib-rituximab arm, versus 14.6 percent in the placebo-rituximab arm. Median overall survival could not be estimated at the time of assessment.

The most common adverse events with copanlisib treatment were increases in blood glucose and blood pressure. These effects are temporary and generally do not require treatment, Matasar noted. "Very few patients had to stop receiving treatment because of these side effects (3 percent and 1 percent,

respectively). Lung inflammation was an adverse event we watched for, but was reported in only 3 percent of patients receiving copanlisib plus rituximab," he said.

Earlier studies using the daily orally administered PI3K inhibitors idelalisib and duvelisib resulted in severe toxicity, including deaths, leading to early termination of clinical trials. Copanlisib is administered intravenously on an intermittent schedule, and has lower rates of such side effects compared with these oral PI3K inhibitors, Matasar said. "Thus, the overall results shown here with CHRONOS-3 are essentially a long-awaited proof of concept for combining a PI3K inhibitor with rituximab, and hopefully offer insight into ongoing and future studies of copanlisib and other investigational PI3K inhibitors in development," he noted.

The primary analysis for this study was triggered when a pre-specified number of events (deaths or progressive disease) was seen, Matasar said. The median follow-up for this primary endpoint was 19 months, and many patients were still on treatment at the time of the analysis. Differences in overall survival, a secondary endpoint of the study, were not seen between arms, and longer follow-up will be required to determine whether copanlisib plus rituximab improves the expected lifespan on average, he added.

This study was sponsored by Bayer AG. Matasar has received honoraria from Bayer AG and subsidiaries of Bayer AG for advising and related activities. Bayer AG also provides research funding for Matasar through MSK. In addition, Matasar has received honoraria from Roche/Genentech for advising and related activities, and the company also provides research funding for him through MSK.

Abstract

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Abstract Body:

Introduction: Rituximab (R)-based therapies are standard for patients (pts) with relapsed advanced iNHL. Copanlisib (C) is a PI3K inhibitor approved as monotherapy for relapsed follicular lymphoma (FL) in pts who have had ≥2 prior systemic therapies. We report primary data from the Phase III CHRONOS-3 study of treatment with C+R *vs* placebo (P)+R in relapsed iNHL (NCT02367040).
Methods: Pts with relapsed iNHL who were progression-free and treatment-free for ≥12 months (mo) after last R-based therapy or unwilling/unfit to receive chemotherapy were randomized 2:1 to receive C+R or P+R. C 60 mg/P was given i.v. on days 1, 8, and 15 (28-day cycle); R 375 mg/m^2 was given i.v. on days 1, 8, 15, and 22 during cycle 1 and on day 1 of cycles 3, 5, 7, and 9. Primary endpoint: centrally assessed progression-free survival (PFS). Secondary endpoints: objective response rate (ORR), duration of response, complete response rate (CRR), overall survival (OS), and treatment-emergent adverse events (TEAEs). The data cut-off date was August 31, 2020.
Results: 307 pts were randomized to C+R and 151 to P+R. FL was the most common lymphoma histology subtype (60.0%), followed by marginal zone (MZL, 20.7%), small lymphocytic (SLL, 10.9%), and lymphoplasmacytic/Waldenström macroglobulinemia (LPL/WM, 8.3%). Median age was 63 years (range 28-91). With a median follow-up of 19.2 mo, the primary study endpoint was met: C+R significantly reduced the risk of disease progression/death *vs* P+R (hazard ratio [HR] 0.52 [95% CI 0.39, 0.69]; 1-sided p=0.000002); median PFS was 21.5 mo (95% CI 17.8, 33.0) *vs* 13.8 mo (95% CI 10.2, 17.5), respectively. Reductions in risk of progression/death were seen across all histology subtypes (HR [95% CI]): FL 0.580 [0.404, 0.833]; MZL 0.475 [0.245, 0.923]; SLL 0.243 [0.111, 0.530]; LPL/WM 0.443 [0.160, 1.231]. ORRs were 80.8% (CRR 33.9%) for C+R and 47.7% (CRR 14.6%) for P+R. Higher ORRs and CRRs were seen across all iNHL subtypes with C+R treatment. Median OS was not estimable. Most common TEAEs (all grades [G]/G3+) in pts receiving C+R were hyperglycemia (69.4%/56.4%), hypertension (49.2%/39.7% [all G3]), and diarrhea (33.6%/4.9% [all G3]). For pts receiving P+R, hyperglycemia (23.3%/8.2% [all G3]), hypertension (19.2%/8.9% [all G3]), neutropenia (16.4%/12.3%), and upper respiratory tract infection (16.4%/0%) were the most common TEAEs. Serious adverse events were higher with C+R (47.2%) *vs* P+R (18.5%). G5 TEAEs occurred in 6 pts (2.0%) receiving C+R (1 [0.3%] deemed treatment-related; pneumonitis) and 1 (0.7%) receiving P+R.
Conclusions: C+R demonstrated broad and superior efficacy *vs* P+R in pts with relapsed iNHL. The safety profile of C+R was manageable and consistent with C and R as monotherapy. Copanlisib is the first PI3K inhibitor to be safely combined with R in relapsed iNHL, representing a potential new therapy option for relapsed iNHL across all subtypes.

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convening more than 30 conferences and educational workshops—the largest of which is the AACR Annual Meeting, with more than 74,000 attendees for the 2020 virtual meetings and more than 22,500 attendees for past in-person meetings. In addition, the AACR publishes nine prestigious, peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research directly as well as in cooperation with numerous cancer organizations. As the Scientific Partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual investigator grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and other policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit www.AACR.org.