Christian Buske[1,2] on behalf of the *iNNOVATE Study group* and the *European Consortium for Waldenström's Macroglobulinemia*

[1]*Comprehensive Cancer Center Ulm, Institute of Experimental Cancer Research, University Hospital of Ulm, Ulm, Germany*
[2]*Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany*

Title: *Final Analysis of the iNNOVATE Study: Ibrutinib/Rituximab vs Placebo/Rituximab*

Background: we have recently shown in the large multinational Phase III randomized iNNOVATE study that the combination of rituximab/ibrutinib is a highly effective and well tolerated treatment regimen, which is significantly superior in treatment outcome compared to placebo/rituximab single agent in treatment naïve and R/R Waldenström's macroglobulinemia (WM). This final analysis presents data after a median follow-up of 50 months of this study.

Methods: in this trial patients had confirmed symptomatic WM, either previously untreated or previously treated; patients with prior rituximab had at least a minor response to their last rituximab-based regimen. Patients were randomly assigned to once-daily ibrutinib 420 mg plus rituximab or placebo plus rituximab (n 5 75 per arm). The primary end point was progression-free survival (PFS). Secondary end points included response rate, time to next treatment, hemoglobin improvement, overall survival, and safety.

Results: Median (95% CI) PFS was not reached (57.7 months to not evaluable) with ibrutinib-rituximab versus 20.3 months (13.0 to 27.6) with placebo/rituximab (P < .0001). PFS benefit was regardless of prior treatment status, MYD88 and CXCR4 mutation status. Higher response rates (partial response or better) were observed with ibrutinib-rituximab (76% v 31% with placebo-rituximab; P < .0001) and were sustained over time. Median time to next treatment was not reached with ibrutinib-rituximab versus 18 months with placebo/rituximab. Median overall survival was not reached in either arm. Ibrutinib/rituximab maintained a manageable safety profile.

Conclusion: After a median follow-up of over 4 years, the data confirm that ibrutinib/rituximab is a highly efficient and safe treatment regimen independently of the MYD88 and CXCR4 status in patients with WM.