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

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Title: *Dexamethasone, Rituximab, and Cyclophosphamide (DRC) versus Bortezomib-DRC (B-DRC) in WM*

Background: Rituximab-Chemotherapy is still one of the cornerstones in the treatment of Waldenström's macroglobulinemia. The ECWM-1 trial of the European Consortium for Waldenström's Macroglobulinemia is testing whether adding Bortezomib to the immunochemotherapy Dexamethasone, Rituximab, Cyclophosphamide improves efficacy in treatment naïve WM preserving the low toxicity profile of DRC.

Methods: the ECWM-1 trial was conducted as a multicenter European randomized phase II trial in treatment naïve patients with WM in need of therapy. Patients were randomized 1:1 to DRC (Dexamethasone 20 mg orally d1, Rituximab 375 mg/m^2 IV d1 cycle 1 and 1400 mg SC d1 cycle 2-6, Cyclophosphamide 100 mg/m^2 x 2 orally d1-5) or to B-DRC (DRC plus Bortezomib SC 1,6mg/m^2 day 1, 8, 15) for 6 cycles (28d interval). Primary endpoint was progression free survival (PFS). Secondary endpoints included response rates, overall survival (OS), and toxicity.

Results: Of 204 registered patients, 2 patients were excluded due to incorrect randomization. Median follow-up was 27.5 months at the time of the data cut. Median age was 68 years (range 34-89) in both arms. After a median follow-up of 27.5 months, the estimated 24-month progression-free survival was 80.6% (95% CI, 69.5 to 88.0) for B-DRC and 72.8% (95% CI, 61.3 to 81.3) for DRC (P 5 .32). At the end of treatment, B-DRC and DRC induced major responses in 80.6% versus 69.9% and a complete response/very good partial response in 17.2% versus 9.6% of patients, respectively. The median time to first response was shorter for B-DRC with 3.0 (95% CI, 2.8 to 3.2) versus 5.5 (95% CI, 2.9 to 5.8) months for DRC. This resulted in higher major response rates (57.0% v 32.5%; P , .01) after three cycles of B-DRC compared with DRC. At best response, the complete response/very good partial response increased to 32.6% for B-DRC. Both treatments were well tolerated: grade $ 3 adverse events occurred in 49.2% of all patients (B-DRC, 49.5%; DRC, 49.0%). Peripheral sensory neuropathy grade 3 occurred in two patients treated with B-DRC and in none with DRC.

Conclusion: This is the largest prospective randomized trial to evaluate bortezomib in combination with standard immunochemotherapy, demonstrating that B-DRC is a well-tolerated regimen which induces a high rate of major responses including deep remissions after 6 months of treatment with a 2-year PFS of 81%,