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

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Title: Combining Bortezomib with Ibrutinib/Rituximab in Waldenström's Macroglobulinemia: results of the ECWM-2 trial of the European Consortium for Waldenström's Macroglobulinemia (ECWM)

Background: both Bortezomib as well as the combination of Ibrutinib/Rituximab have shown remarkable activity in the treatment of Waldenström's macroglobulinemia. The ECWM-2 trial of the European Consortium for Waldenström's Macroglobulinemia (NCT03620903) tested the tolerability and efficacy of Bortezomib-Ibrutinib/Rituximab (B-IR) as first line treatment in WM.

Methods: the ECWM-2 trial was conducted as a multicenter European single-arm phase II trial in treatment naïve patients with WM in need of therapy. The treatment combined Bortezomib (1.6 mg/ m^2 s.c. d1,8,15) with Rituximab (375 mg/m^2 i.v (C1d1), 1400 mg absolute s.c (C2-6 d1) and Ibrutinib (420 mg p.o. daily) for 6 cycles (d=28). This was followed by maintenance with Rituximab (1400 mg absolute s.c; D1 every 2nd month) plus Ibrutinib for 24 months and subsequent ibrutinib treatment until progression or non-tolerated toxicity.

Results: 53 patients were included. Median age was 63 years (range 36-84), 62% were male and 70% of patients had intermediate/high risk according to the ISSWM prognostic score. B-IR reduced rapidly deep responses within three months of treatment. No progression was observed so far after a median follow-up of 37 months. There have been 8 deaths in the course of the study in total, 5 caused by COVID-19 and three caused by respiratory tract infection.

Conclusion: B-IR shows high efficacy in WM, characterizing this treatment regimen as a novel and highly potent treatment option for patients with WM. Most of the deaths were due to COVID-19, reflecting recruitment for this trial in the COVID-19 pandemic.