R2W: Subcutaneous Bortezomib, Cyclophosphamide and Rituximab (BCR) versus Fludarabine, Cyclophosphamide and Rituximab (FCR) for initial therapy of Waldenstrőm's macroglobulinaemia (WM): a randomised phase II study (NCT01592981).

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Earlier studies have indicated that the combination of bortezomib and rituximab is highly active in WM. However, there is scope to further improve the response rate. We evaluated the addition of cyclophosphamide to bortezomib and rituximab in previously untreated patients with WM.

Symptomatic treatment-naïve patients were enrolled into this prospective randomised (2:1), multicentre, non-comparative Phase II study and stratified according to the International Prognostic Scoring System for WM. Patients were treated with BCR (Bortezomib 1.6 mg/m^2 s.c. days 1, 8, 15; Cyclophosphamide 250 mg/m^2 oral days 1, 8, 15; Rituximab 375mg/m^2 i.v. days 1, 8, 15, 22 cycles 2 and 5 only) or FCR (Fludarabine 40mg/m^2 oral days 1-3; Cyclophosphamide 250 mg/m^2 oral days 1-3; Rituximab 375mg/m^2 i.v. days 1, 8, 15, 22 cycles 2 and 5 only) for 6 cycles repeated every 28 days. The primary endpoint was investigator assessed overall response rate (ORR) using consensus criteria.

Sixty patients were enrolled into this study and 59 received trial treatment (BCR=42, FCR=17). 73% were male, median (range) age was 67 years (43-87), Haemoglobin 9.8 g/dL (6.5-14.0), serum IgM paraprotein 34 g/L (3.2-80.2), plasma viscosity 3.6 mPa.s (2.0-9.3) and 25/30/45% were low/intermediate/high risk respectively. ORR was 97.6% in BCR patients with 78.6% achieving a major response (CR=1, VGPR=8, PR=24, MR=7, SD=1), one patient was not assessed as no evidence of WM was found upon central review; 82.4% in FCR patients with a major response rate of 76.5% (CR=0, VGPR=3, PR=10, MR=1, SD=2), one patient stopped treatment after cycle 1 due to continuing cytopenia (grade 4). To date with a median follow up of 40.7 months, 40 patients were progression-free; 11 patients progressed (all BCR) and 8 patients died (1 BCR; 7 FCR). There were 3 deaths from myelodysplastic syndrome (MDS) (all FCR). Grade 3 or higher toxicities included anemia (5 [11.9%] BCR; 3 [17.6%] FCR), neutropenia (11 [26.2%] BCR; 12 [70.6%] FCR), thrombocytopenia (7 [16.7%] BCR; 6 [35.3%] FCR) and infection (2 [4.8%] BCR; 5 [29.4%] FCR). No grade 3 or higher neuropathy was reported.

BCR and FCR are both highly effective treatments for primary therapy of WM but FCR is associated with increased toxicity and concerning incidence of secondary MDS.