Treatment of relapsed/refractory Waldenström Macroglobulinemia patients: preliminary clinical and molecular results of the phase II BRB (Bendamustine, Rituximab and Bortezomib) trial of the Fondazione Italiana Linfomi (FIL)

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Introduction: Symptomatic patients with relapsed/refractory Waldenström Macroglobulinemia (RR-WM) after one line of therapy and treated with standard rituximab plus chemotherapy salvage treatment, show a 18-months progression free survival (PFS) of about 50%. On behalf of the Fondazione Italiana Linfomi, a multicenter phase II study was designed to assess whether a combination of bendamustine, rituximab and bortezomib (BRB), could be considered a promising treatment.

Patients and Methods: This single-arm phase II study tested the hypothesis that 18-months PFS is at least 65%. The required sample size was 38 patients (alpha=0.10; beta=0.25; minimum follow up=24 months).

Patients were treated with rituximab 375 mg/m2 intravenously on day 1 followed by intravenously bendamustine 90 mg/m2 on day 1 and 2 and subcutaneous bortezomib 1.3 mg/m2 on day 1, 8, 15 and 22, every 28 days for 6 months.

In the last 22 patients MYD88^{L265P} was tested by the recently described droplet digital PCR (ddPCR) assay both on bone marrow (BM) and peripheral blood (PB) samples, both at baseline (as mutational screening) and at the end of treatment (for minimal residual disease purposes, MRD).

Results: Median age was 66 years (8 patients were older than 75 years). Many patients had features of advanced disease such as cytopenia (anemia 71%, thrombocytopenia 20%), systemic symptoms (40%) and symptomatic splenomegaly (24%). Sixteen (42%) patients had at least one comorbidity, mostly cardiovascular disease (18%) or metabolic disorders, such as diabetes mellitus (16%).

At the time of analysis, 26 patients completed the six cycles of therapy, six pts stopped therapy for toxicity and six pts are still being treated. On an intention-to-treat analysis (N=32), overall response rate was 75%, including 3 (9%) complete, 10 (31%) very good partial, 10 (31%) partial responses and 1 (3%) minimal response according to IWM response criteria. We observed four progressions and two deaths without progression (one cerebrovascular accident during the fifth cycle and one pulmonary embolism at three months follow up). Overall, treatment was well tolerated, 13 patients (34%) experiencing grade 3-4 neutropenia, especially in cycle 4 (leading in four cases to treatment discontinuation) and only two patients experiencing cutaneous toxicity related to bendamustine. Nervous system disorders was observed in 5 patients (13%; 4 of grade 1-2 and 1 of grade 3-4), with no discontinuations.

All the 22 patients assessed for MYD88^{L265P} at baseline scored positive in BM, while only 18/22 (82%) in PB, prospectively confirming the risk of false negative results when only PB of rituximab pre-treated patients is analyzed. Among the 16 patients monitored for MRD after treatment 5 scored negative in BM and 9 in PB, highlighting the deep activity of the BRB regimen in clearing the disease.

Conclusion: The preliminary results showed that BRB regimen is a well-tolerated salvage treatment for RR-WM patients after first line of therapy. Moreover, the deep anti-tumor activity of this regimen is highlighted by the promising rates of both clinical and molecular responses. As the analyses on the last enrolled patients are still ongoing, more complete and mature results will be presented during the meeting.