P1159 A MULTICENTER, INTERNATIONAL COLLABORATIVE STUDY EVALUATING FRONTLINE THERAPY WITH BENDAMUSTINE RITUXIMAB FOR WALDENSTRÖM MACROGLOBULINEMIA

**Topic:** 18. Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

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**Background:** Bendamustine rituximab (BR) is a frequently used chemoimmunotherapy for indolent lymphomas, including Waldenström macroglobulinemia (WM), a rare B-cell malignancy. The promising results of a small subset analysis (n= 41) of the Study group indolent Lymphomas (StiL) trial, demonstrating a median progression-free survival (PFS) of 69.5 months in the frontline setting served as the basis for widespread adoption of BR. Whether the more recently identified somatic mutations within the MYD88 and CXCR4 genes impact the outcomes of patients (pts) treated with BR remains less clear.

**Aims:** To study a large cohort of BR-treated pts with active WM through an international, multicenter collaborative effort.

**Methods:**

Records of pts with newly diagnosed active WM who received BR between January 2012 and July 2021, in the US and Europe, were reviewed. The MYD88L265P and CXCR4 mutation status were captured, if available. All time-to-event analyses were performed from the frontline therapy initiation, using the Kaplan-Meier method.

**Results:**

Among 248 pts who were treated with BR, 208 pts received BR induction without rituximab maintenance, and were included in the primary analysis. The median age at treatment initiation was 65 (range 40-86) years; 64 % were males. The baseline characteristics are outlined in Table 1. The median follow-up was 4 (95% CI: 3.6-4.6) years.

The estimated median PFS was 5.9 years [95% CI: 5.3-not reached (NR)]. The estimated 5-year overall survival (OS) rate was 90%. Among 174 pts evaluable for response, the overall response rate (ORR), major response rate (MRR) and very good partial response (VGPR) rates were 95%, 93% and 31%, respectively, per the modified IWWM-6 criteria based on serum IgM level alone. Pts with progression of disease (POD) within 24 months of BR therapy (11%) had an inferior subsequent survival compared to those without POD within 24 months, the reference group [5-year subsequent survival rate, 71 % versus (vs) 86%, p=0.02].

Among 131 (63%) pts with a known MYD88L265P status, 88% (n=116) had MYD88L265P genotype. The 4-year PFS was 71% for both pts with MYD88L265P and MYD88WT genotypes (p=0.44), Figure 1A. The VGPR rates were also comparable between the two groups (41% for MYD88L265P and 50% for MYD88WT genotypes, p=0.55). Among 42
(20%) pts with a known CXCR4 mutation status, 28% harbored a CXCR4 mutation. The ≥VGPR rate for pts with CXCR4<sup>MUT</sup> genotype was numerically lower; 33% vs 57% for those with CXCR4<sup>WT</sup> genotype, p=0.3. A trend towards shorter PFS among pts with CXCR4<sup>MUT</sup> genotype [estimated median PFS for 3.9 years (95% CI: 0.8-NR) vs 5.5 years (95% CI 5.3-NR) for pts with CXCR4<sup>WT</sup> genotype, p=0.05, Figure 1B] was observed. The PFS rates for pts without a known MYD88 or CXCR4 mutational status was comparable to their counterparts with known genotypes, respectively.

Among 40 (16%) pts who had received rituximab maintenance following BR, the median age at initiation of therapy was 67 years (range 44-88). After 1:1 matching for age, the 4-year PFS for the rituximab maintenance group was 89% vs 73% for pts who did not receive rituximab maintenance (p=0.09); OS was comparable (5-year OS rate, 85% for both groups, p=0.99).

### Summary/Conclusion:

Fixed-duration BR is a highly effective regimen for pts with previously untreated symptomatic WM, irrespective of the MYD88<sup>L265P</sup> mutation status, although early POD, within 2 years of initiation of BR, is associated with inferior subsequent survival. Our preliminary analysis, suggesting that the presence of CXCR4 mutation confers resistance to BR, warrants confirmation in prospective studies.

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**Table 1.** Baseline characteristics at initiation of Bendamustine-Rituximab without rituximab maintenance

| Parameter                      | Median (interquartile range) |
|-------------------------------|-----------------------------|
| Serum IgM, mg/dL              | 2095 (1555-5526)            |
| Serum IgM spike, g/dL         | 2.6 (1.3-4.1)               |
| Hemoglobin, g/dL              | 9.8 (8.3-11.2)              |
| Platelet count, x 10<sup>9</sup>/L | 290 (111-138)              |
| Beta-2 microglobulin, mg/L    | 3.6 (2.5-5.2)               |
| Lactate dehydrogenase > upper limit of normal, % | 14% |
| Bone marrow lymphoplasmacytic infiltrate, % | 66 (30-80) |
| Serum IgG<sub>c</sub>, mg/dL   | 574 (280-1855)              |
| Serum IgG<sub>c</sub> spike, mg/dL | 319 (79-90)               |
| Involved/uninvolved serum free light chain<sup>+</sup> ratio | 7.2 (1.0-44.7) |

International prognostic scoring system for WM

- Low Risk: 15%
- Intermediate Risk: 49%
- High Risk: 46%

*Numbers rounded up.*