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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Prospective Evaluation of Minimal Residual Disease in Waldenström Macroglobulinemia across Different Tissues and Treatments: Results of the "BIO-WM" Trial of the Fondazione Italiana Linfomi (FIL)

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Introduction. *MYD88* ^{L265P} is the hallmark mutation in Waldenström Macroglobulinemia (WM) and is becoming increasingly important in the management of IgM-gammopathies, due to its role as prognostic and predictive biomarker. Recently, *MYD88* ^{L265P} detection by allele-specific quantitative PCR was proposed as reliable minimal residual disease (MRD) marker in bone marrow (BM) samples (Varettoni, Hematol Oncol 2022). Novel, more sensitive, techniques as droplet digital PCR (ddPCR) might extend the feasibility of MRD detection in WM also in non-invasive tissues, as peripheral blood (PB) or plasmatic cell-free (cf) DNA. This was a secondary endpoint of the multicenter, observational "BIOWM" (NCT03521596) trial, sponsored by the Fondazione Italiana Linfomi (FIL) and the International WM Foundation/Leukemia and Lymphoma Society. From 2018 to 2020 this trial enrolled 300 consecutive patients with primary diagnosis of WM or IgM-MGUS and a systematic biobanking was performed. Here are presented the first results of the MRD study on the patient subset who received frontline treatment, with the aim of driving correlations with clinical response, type of therapy received and outcome prediction. **Methods.** Paired

BM, PB and plasma samples were collected for each patient at baseline (T0) and follow-up and *MYD88* ^{L265P} detection was performed by ddPCR in all specimens (Drandi, Haematologica 2018). As of today, 59/300 patients (58 WM and 1 IgM-MGUS) received frontline treatment and MRD levels after therapy (T2) were detected by ddPCR: actually, T0-T2 paired samples were available in 49 (BM), 56 (PB) and 48 (cfDNA) cases, respectively. Moreover, MRD was evaluated also by 8-color multiparametric flow cytometry (MFC) in 23 BM and 24 PB samples with a minimum of 10 million cells acquired. **Results.** Median age of the 59 treated patients was 68 years (24-85), 32% were female, median IgM value was 2420 mg/dL (101-8840), median Hb 10.5 g/dL (8 -17) and IPSS-WM was high in 35% and intermediate in 46%. *MYD88* ^{L265P} mutation rate was 94% (46/49) in BM, 80% (45/56) in PB and 90% (43/48) in cfDNA samples, respectively. Treatment was started because of anemia in 32% cases, lymphadenopathy or splenomegaly in 34%, hyperviscosity in 20%, other reasons in 13%, and the only MGUS patient required treatment for anti-myelin-associated glycoprotein polyneuropathy. Thirty-one out of 59 patients received bendamustine-rituximab (BR), 23/59 dexamethasone, rituximab and cyclophosphamide (DRC) or DRC-like regimen and 5/59 a single agent therapy (namely, 3 rituximab, 1 cyclophosphamide, 1 ibrutinib). Overall response rate was 90% (87% for BR and 96% for DRC), with 19% CR, 29% VGPR and 35% PR in BR and 4% CR, 0% VGPR and 91% PR in DRC, respectively. Overall, MRD negativity after treatment was 30% (14/46) in BM, 89% (40/45) in PB and 54% (23/43) in cfDNA, respectively. Moreover, among patients still MRD positive after treatment, median *MYD88* ^{L265P}tumor burden shrinkage was about 2 Logs in BM (5.5E-03 vs 2.1E-01) and around 1 Log in cfDNA (5.9E-03 vs 3.7E-02) and in PB samples (3.6E-03 vs 2.5E-02), respectively (Figure 1). Interestingly, the MRD shrinkage in BM was deeper among patients receiving BR (48% MRD negative with a median *MYD88* ^{L265P} decrease of more than 2 Logs among patients still MRD positive) vs patients receiving DRC (10% MRD negative with a median decrease of 1 Log), Figure 2. Similar trends in favor of BR in inducing MRD negativity were reported in PB (96% vs 88%) and cfDNA (70% vs 35%), respectively. MRD results by MFC were overall in line with ddPCR results: namely 27% of patients reached MRD negativity in BM and 69% in PB. The median follow-up for the whole series was 41 months, resulting in a 3-years PFS of 71% and 3-years OS of 89%, respectively. Interestingly, despite the current limited follow-up for such an indolent disease, MRD positivity by ddPCR in PB predicted a dismal clinical outcome if compared with MRD negative patients (3-years PFS 40% vs 73%, p=0.038). **Conclusions.** To the best of our knowledge, this is the first report of prospective MRD evaluation in a WM clinical trial. Our preliminary results suggest that *MYD88* ^{L265P} monitoringby ddPCR is a suitable target for MRD analysis, in the contest of common immunochemotherapeutic schedules. Moreover, different levels of disease persistence were described across BM, PB and cfDNA, with MRD monitoring in non-invasive tissues showing promising predictive value for outcome discrimination.

Disclosures Cavallo: *Beigene:* Research Funding; *Takeda:* Research Funding; *Astra Zeneca:* Research Funding; *Roche:* Honoraria, Speakers Bureau. **Laurenti:** *AstraZeneca:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees; *Beigene:* Membership on an entity's Board of Directors or advisory committees. **Puig:** *Takeda:* Consultancy, Honoraria, Other, Research Funding; *Amgen:* Consultancy, Honoraria, Other, Research Funding; *BMS:* Consultancy, Honoraria, Other, Research Funding, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Other, Research Funding; *Pfizer:* Research Funding; *Sanofi:* Consultancy, Honoraria; *The Binding Site:* Consultancy, Honoraria. **Garcia-Sanz:** *Gilead/Kite:* Consultancy, Honoraria, Other: TRAVEL, ACCOMMODATIONS, EXPENSES, Research Funding; *Takeda:* Consultancy, Honoraria, Other: TRAVEL, ACCOMODATIONS, EXPENSES, Research Funding, Speakers Bureau; *Eusa Pharma:* Honoraria; *Novartis:* Consultancy, Honoraria; *Kyowa Kirin:* Consultancy; *Incyte:* Consultancy, Honoraria; *Lilly:* Consultancy; *ADC Therapeutics America:* Consultancy; *Miltenyi:* Consultancy; *Ideogen:* Consultancy; *Abbvie:* Consultancy; *BeiGene:* Consultancy, Honoraria, Other: TRAVEL, ACCOMODATIONS, EXPENSES, Speakers Bureau; *Roche:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria, Other: TRAVEL, ACCOMMODATIONS, EXPENSES, Research Funding, Speakers Bureau; *BMS/Celgene:* Consultancy, Honoraria, Other: TRAVEL, ACCOMMODATIONS, EXPENSES; *invivo scribe (IVS):* Patents & Royalties. **Varettoni:** *ASTRAZENECA:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *BEIGENE:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *JANSSEN:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *ABBVIE:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Ferrero:** *Janssen:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *EUSA Pharma:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Abbvie:* Consultancy; *Sandoz:* Consultancy; *Beigene:* Research Funding; *Morphosys:* Research Funding; *Incyte:* Membership on an entity's Board of Directors or advisory committees; *Clinigen:* Membership on an entity's Board of Directors or advisory committees; *Servier:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Gentili:* Speakers Bureau; *Italfarmaco:* Membership on an entity's Board of Directors or advisory committees.

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Figure 1. MRD shrinkage across different tissues. *MYD88*^{L265P} values in bone marrow (BM), peripheral blood (PB) and plasma cfDNA (PL) at baseline (T0) and after treatment (T2) are depicted. MRD, minimal residual disease; DRC, dexamethasone, rituximab and cyclophosphamide.

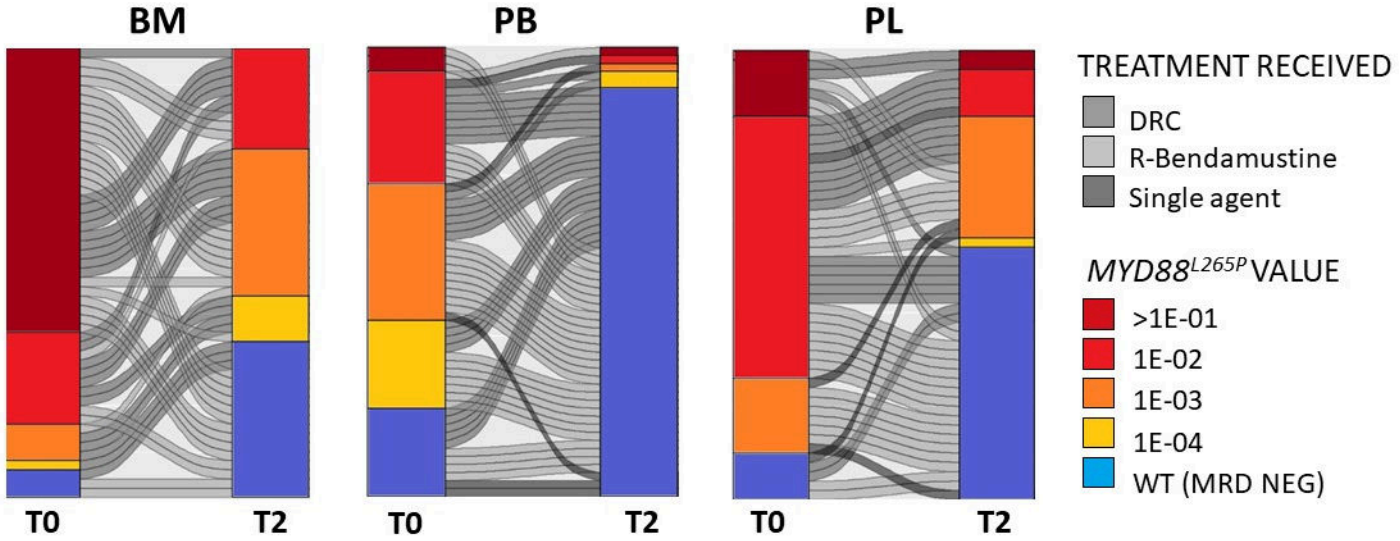

Figure 2. Waterfall plot describing MRD shrinkage in BM according to treatment received. Decrease in *MYD88*^{L265P} values in bone marrow (BM) after therapy is depicted. Best response rates from R-Bendamustine and DRC are indicated for each patient. MRD, minimal residual disease; DRC, dexamethasone, rituximab and cyclophosphamide; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease.

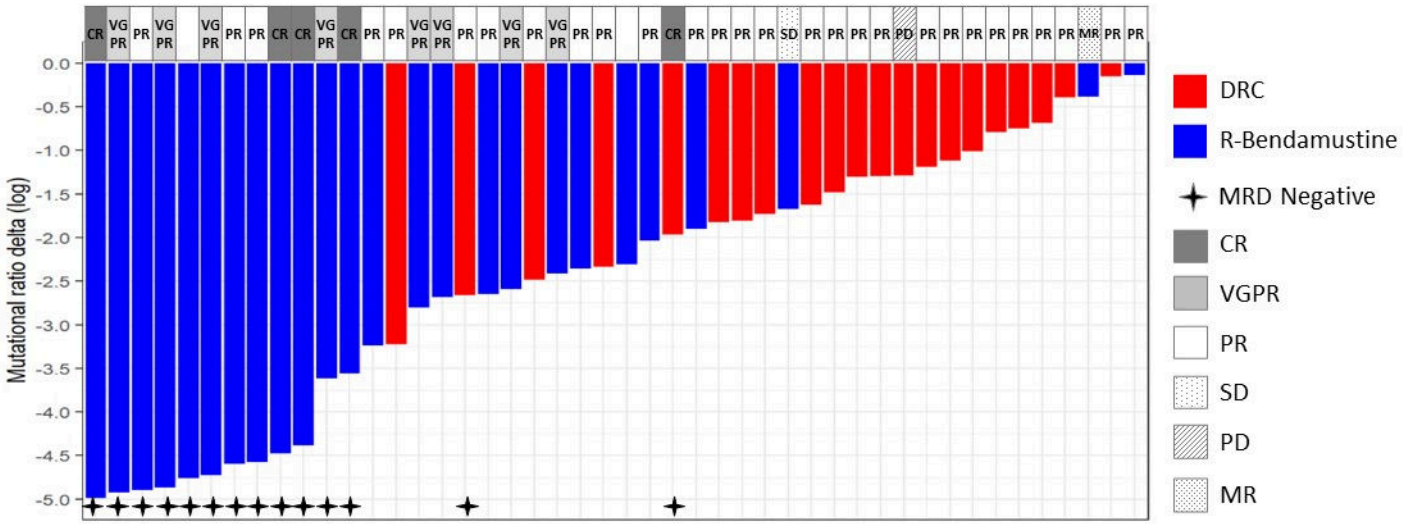

Figure 1