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POSTER ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Analysis of Peripheral Blood and Bone Marrow Residual Disease Dynamics during Intensive Treatment and Maintenance in Patients with Multiple Myeloma Included in the GEM12MENOS65 and GEM14MAIN Clinical Trials

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Introduction: In patients (pts) with multiple myeloma (MM), analysis of minimal residual disease (MRD) dynamics in bone marrow by Next Generation Flow Cytometry (NGF) has shown that conversion of minimal residual disease (MRD) status modulates the risk of progression. Mass spectrometry measuring low-level monoclonal immunoglobulins has shown potential for Peripheral-blood based Residual Disease (PRD) assessment. In this study, we have analyzed the clinical impact of PRD and MRD dynamics in MM pts receiving intensive treatment as per the GEM2012MENOS65 trial and during maintenance as per the GEM2014MAIN trial.

Patients and Methods: In GEM2012MENOS65 trial, pts received six cycles of VRD-GEM induction, autologous stem cell transplantation conditioned with melphalan or busulfan plus melphalan and consolidation with two cycles of VRD-GEM. Patients achieving at least minimal response were offered to be enrolled in the GEM2014MAIN and randomized to maintenance with lenalidomide and low-dose dexamethasone (Rd) or Rd plus ixazomib for two years; if not reaching MRD negativity at this point, pts received three more years of Rd. PRD dynamics were analyzed separately in each trial by Quantitative Immunoprecipitation Mass Spectrometry with anti IgG/A/M, total k and total l beads using the EXENT ® Solution (The Binding Site, part of Thermo Fisher Scientific). MRD was analyzed following the recommendations of the IMWG and according to the Euroflow guidelines. Only those pts with available samples at all the time points analyzed (GEM2012: post-induction, post-ASCT and after-consolidation; GEM014: post-consolidation and after 1 and 2 years of maintenance) were included.

Results: 134 out of the 458 pts enrolled in the GEM2012MENOS65 trial and receiving intensive treatment as per protocol were analyzed. At treatment completion (post-consolidation), PRD and MRD status were associated with almost identical prognostic value: median progression-free survival (mPFS) in PRD $^{-}$ not reached (n.r.) *vs* 3.98 years in PRD $^{+}$ cases (p=0.0006) and in MRD $^{-}$ n.r. *vs* 3.99 years in MRD $^{+}$ cases (p=0.0001).

When dynamics were analyzed, sustained PRD and MRD negativitywas observed in 58 (43.3%) and 44 (33.8%) pts and sustained positivity in 42 (31.2%) and 57 (42.5%) pts, respectively. In 35 (26.1%) and 33 (24.6%) pts, PRD and MRD converted from positive to negative, respectively. Sustained PRD or MRD positivity at the 3 time points analyzed was associated with a significantly shorter PFS (mPFS 4.04 years, p=0.0042 and 3.9 years, p=0.0008, respectively), compared to pts remaining negative or converting from positive to negative, in whom mPFS was not reached (Fig.1A).

109 pts out of the 332 pts enrolled in the GEM2014MAIN trial and receiving maintenance treatment as per protocol were analyzed. At treatment completion (after two years of maintenance), PRD or MRD status were associated with comparable prognostic value: mPFS in PRD $^{-}$ and PRD $^{+}$ cases n.r. (p=0.0039) and in MRD $^{-}$ cases n.r. *vs* MRD $^{+}$ 2.87 years (p<0.0001).

When dynamics were analyzed, sustained PRDand MRD negativity was observed in 68 pts (62.4%) and 61 (55.9%) pts and sustained positivity in 19 (17%) and 19 (17%) cases, respectively. In 17 (15.6%) pts PRD and MRD converted from positive to negative and in 5 (5.6%) and 10 (0.91%) from negative to positive, respectively. Sustained PRD positivity at the 3 time points analyzed was associated with a shorter PFS (p=0.0185), compared to pts who remained PRD $^{-}$ or converted from PRD $^{+}$ to PRD $^{-}$, in whom mPFS was not reached. The mPFS in pts remaining MRD $^{-}$ or converting from MRD $^{+}$ to MRD $^{-}$ was similar and has not been reached yet; the mPFS in pts with sustained MRD positivity at the 3 time points analyzed or converting from MRD $^{-}$ to MRD $^{+}$ was also similar (2.99 years and 2.88 years, respectively). Interestingly, pts converting from PRD $^{-}$ to PRD $^{+}$ had a poorer PFS (mPFS of 0.86 years) as compared to patients converting from MRD $^{-}$ to MRD $^{+}$ (mPFS of 2.28 years) (Fig.1B).

Conclusions: In conclusion, assessment of PRD and MRD dynamics during intensive treatment and maintenance allows to define more precisely the patients' clinical outcome as compared to the analysis of isolated time points. Reaching MRD or PRD negativity post-consolidation or after 2 years of maintenance is associated with a similar prognostic value, thus highlighting the clinical utility of mass spectrometry as an alternative, non-invasive technique for disease evaluation.

Disclosures Puig: *The Binding Site:* Consultancy, Honoraria; *Sanofi:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria, Other, Research Funding; *Janssen:* Consultancy, Honoraria, Other, Research Funding; *BMS:* Consultancy, Honoraria, Other, Research Funding, Speakers Bureau; *Amgen:* Consultancy, Honoraria, Other, Research Funding; *Pfizer:* Research Funding. **Agullo:** *The Binding Site:* Consultancy, Honoraria, Research Funding. **Contreras:** *The Binding Site:* Consultancy, Honoraria. **Paiva:** *Roche Glycart AG:* Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria; *Sanofi:* Consultancy, Honoraria, Research Funding; *EngMab:* Research Funding; *GSK:* Honoraria, Research Funding; *Takeda:* Honoraria, Research Funding; *Adaptive:* Honoraria; *Amgen:* Honoraria; *Bristol-Myers Squibb:* Consultancy, Honoraria, Research Funding; *Gilead:* Honoraria; *Oncopeptides:* Honoraria. **Cedena:** *BMS:* Honoraria; *Abbvie:* Honoraria; *Janssen:* Honoraria. **Rosiñol:** *Takeda:* Other: Honoraria for lectures; *GlaxoSmithKline:* Other: Honoraria for lectures; *Sanofi:* Other: Honoraria for lectures; *Amgen:* Other: Honoraria for lectures; *Bristol Myers Squibb/Celgene:* Other: Honoraria for lectures; *Janssen:* Other: Honoraria for lectures. **Garcia-Sanz:** *Novartis:* Consultancy, Honoraria; *Kyowa Kirin:* Consultancy; *Incyte:* Consultancy, Honoraria; *Lilly:* Consultancy; *ADC Therapeutics America:* Consultancy; *Miltenyi:* Consultancy; *Ideogen:* Consultancy; *Eusa Pharma:* Honoraria; *Gilead/Kite:* Consultancy, Honoraria, Other: TRAVEL, ACCOMMODATIONS, EXPENSES, Research Funding; *Janssen:* Consultancy, Honoraria, Other: TRAVEL, ACCOMMODATIONS, EXPENSES, Research Funding, Speakers Bureau; *BMS/Celgene:* Consultancy, Honoraria, Other: TRAVEL, ACCOMMODATIONS, EXPENSES; *Roche:* Consultancy, Honoraria; *Abbvie:* Consultancy; *BeiGene:* Consultancy, Honoraria, Other: TRAVEL, ACCOMODATIONS, EXPENSES, Speakers Bureau; *invivo scribe (IVS):* Patents & Roy-

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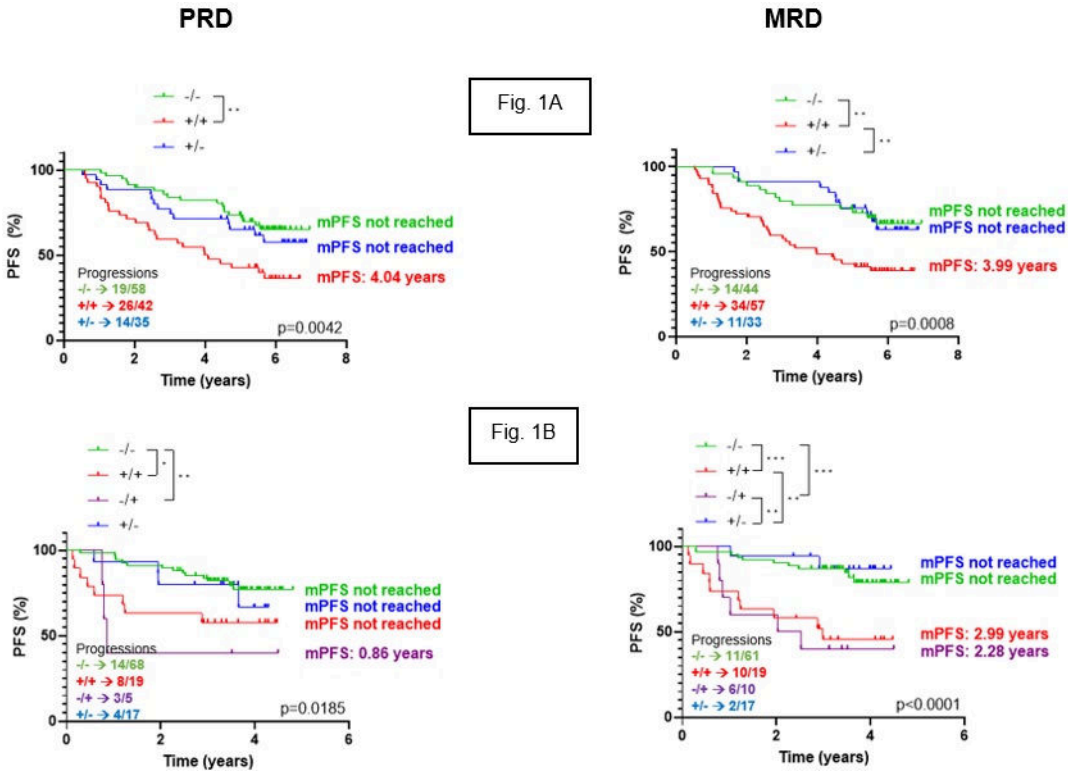

Figure 1

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