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ORAL ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Minimally Invasive Assessment of Measurable Residual Disease (MRD) in Multiple Myeloma (MM)

Carmen Gonzalez, MS[1], *Marta Lasa, PhD*[1], *Laura Notarfranchi*[2,1], *Cristina Agullo*[3], *Natalia Buenache Cuenda*[4], *Anastasiia Zherniakova*[1], *Sergio Castro*[3], *José Juan Pérez*[3], *Veronica Gonzalez-Calle, MD PhD*[3], *Maria Teresa Cedena Romero, MD PhD*[4], *Santiago Barrio*[4,5], *Alejandro Martín-Muñoz*[4,5], *Leire Burgos*[1], *Diego Alignani*[1], *Maria Jose Calasanz, PhD*[1], *Paula Rodriguez Otero, MD PhD*[1], *Laura Rosiñol, MD PhD*[6], *Felipe De Arriba, MD PhD*[7], *Enrique M Ocio, MD PhD*[8], *Albert Oriol Rocafiguera, MD*[9], *Luis Palomera, MD PhD*[10], *Yolanda González-Montes, MD*[11], *Anna Maria Sureda Balari, MD PhD*[12], *Miguel Teodoro Hernandez Garcia*[13], *Maria Esther Clavero Sanchez*[14], *Angela Ibanez Garcia*[15], *Clara Gomez, MD*[16], *Alberto Orfao, MD PhD*[17], *Maria Victoria Mateos, MDPhD*[3], *Juan Jose Lahuerta Palacios*[4], *Joan Bladé, MD PhD*[6], *Jesus San-Miguel, MD PhD*[1], *Joaquin Martinez-Lopez, MD PhD*[4], *Noemi Puig, MDPhD*[3], *Bruno Paiva*[1]

[1] Cancer Center Clinica Universidad de Navarra, Centro de Investigación Médica Aplicada (CIMA), IDISNA, CIBER-ONC number CB16/12/00369 and CB16/12/00489, Pamplona, Spain
[2] University of Parma, Parma, ITA
[3] Hospital Universitario de Salamanca, Instituto de Investigacion Biomedica de Salamanca (IBSAL), University of Salamanca, Salamanca, Spain
[4] Hospital Universitario 12 de Octubre, CIBER-ONC CB16/12/00369, CNIO, Madrid, Spain
[5] Altum Sequencing Co., Madrid, Spain
[6] Amyloidosis and Multiple Myeloma Unit, Department of Hematology, IDIBAPS, Hospital Clinic, Barcelona, Spain
[7] Hospital Morales Meseguer, IMIB-Arrixaca, Universidad de Murcia, Murcia, Spain
[8] Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain
[9] Institute of Oncology and Josep Carreras Institute, Hospital Germans Trias i Pujol, Badalona, Spain
[10] Hospital Clinico Universitario Lozano Blesa, Instituto Investigacion Sanitaria Aragon, Zaragoza, Spain
[11] Institut d'Oncologia Dr. Josep Trueta, Girona, Spain
[12] Hospital Duran i Reynals, Institut d'Investigacio Biomedica de Bellvitge (IDIBELL), Universitat de Barcelona, Barcelona, Spain, Barcelona, Spain
[13] Hospital Universitario de Canarias, La Laguna. Santa Cruz De Tenerife, ESP
[14] Hematology, Hospital Virgen de las Nieves, Granada, ESP
[15] Hematology Department, Complejo Hospitalario Universitario de Albacete, Albacete, ESP
[16] Hospital Universitario de Galdakao, Galdakano, Spain
[17] Cancer Research Center (IBMCC-CSIC/USAL-IBSAL), Cytometry Service (NUCLEUS) and Department of Medicine, University of Salamanca, Salamanca, Spain

BACKGROUND
MRD is an established test in MM clinical trials but not in routine practice. A hindrance to its wider adoption is invasive bone marrow (BM) aspirates. Thus, the possibility of assessing MRD using minimally invasive methods could be paramount to facilitate its transition from clinical trials to routine practice, but also to improve patients' (pts) quality of life and to generate more meaningful MRD results based on periodic assessments instead of limited time points. However, the methods developed for MRD evaluation in BM are less sensitive when used in peripheral blood (PB).

AIM
Investigate the complementarity and prognostic value of new multimodal minimally invasive MRD assessment in MM.

METHODS
This study included 243 transplant eligible and ineligible pts who were on maintenance or observation at the time of MRD assessment in PETHEMA/GEM clinical trials. In all cases, MRD was evaluated in PB using BloodFlow, which is a highly sensitive method (10^{-7}) that combines immunomagnetic enrichment with next-generation flow (NGF) cytometry. Periodic assessment of MRD in peripheral blood (PB) using BloodFlow was performed every six months. In 27 patients, MRD was further investigated

in cfDNA using CloneSight, a highly sensitive (10^{-4}) next-generation sequencing method based on pt-specific mini-panels of multiplexed amplicons covering somatic mutations identified at diagnosis. In 169 of the 243 patients, MRD was analyzed in the serum using Quantitative Immunoprecipitation Mass Spectrometry (QIP-MS) with anti-IgG/A/M, total κ and λ beads.

RESULTS

BloodFlow was performed in a total of 867 PB samples, out of which 77 (9%) were MRD positive. The median number of CTCs/μL was 0.016 (range, 0.0003 - 0.29). In 506 of the 867 assessments, MRD was simultaneously analyzed in the BM using NGF. The concordance between BloodFlow in PB and NGF in BM was 78.9% (70.4% double negative and 8.5% double positive MRD results). The frequency of BloodFlow-/NGF+ and BloodFlow+/NGF- discordant assessments was 20.3% and 0.8%, respectively.

Serial assessment of MRD in PB using BloodFlow showed that 221 of the 243 (91%) pts had sustained MRD negativity and 13 (5%) were persistently positive. MRD conversions from negative to positive were noted in 9 (4%) pts. The landmark median PFS from the latest MRD assessment was not reached (NR) vs 3 months in negative vs positive patients (HR: 0.09, $P < .001$). Of note, only 11 of the 221 (5%) MRD negative pts relapsed thus far.

Of the 27 pts in whom MRD was simultaneously analyzed in cfDNA using CloneSight, five were MRD positive. The landmark median PFS from the latest MRD assessment was NR vs 5 months in negative vs positive pts (HR: 0.23, $P = .057$). The number of patients with BloodFlow-/CloneSight-, BloodFlow+/CloneSight-, BloodFlow-/CloneSight+ and BloodFlow+/CloneSight+ results were 17, 5, 2 and 3. The landmark median PFS from the latest MRD assessment in patients with double negative MRD vs positive by either method was NR vs 8 months (HR: 0.20, $P = .056$). Of note, only 2 of the 17 double negative MRD patients relapsed thus far.

Of the 169 pts in whom MRD was simultaneously analyzed in serum using QIP-MS, 37 (22%) were MRD positive. The landmark median PFS from the latest MRD assessment was NR in negative and positive patients (HR: 0.13, $P < .001$). The number of patients with BloodFlow-/QIPMS-, BloodFlow+/QIPMS-, BloodFlow-/QIPMS+ and BloodFlow+/QIPMS+ results were 130, 2, 26 and 11. The landmark median PFS from the latest MRD assessment in patients with double negative MRD vs positive by either method was NR and 8 months, respectively (HR: 0.07, $P < .001$). Of note, only 3 of the 130 (2%) double negative MRD patients relapsed thus far. The negative predictive value (NPV) of a double negative MRD detection in PB/serum using BloodFlow/QIP-MS and MRD negativity in BM using NGF was 86%.

CONCLUSIONS

This is the first study of multimodal minimally invasive MRD assessment in MM. Our results show that BloodFlow, CloneSight and QIP-MS are empowered to detect MRD with high sensitivity in PB, cfDNA and serum. The presence of CTCs, mutations and M-component was systematically associated with dismal PFS. The complementarity between these methods achieved a high NPV of MRD negativity in BM, and enabled the identification of multimodal MRD negative pts with very low risk of relapse. Thus, this study paves the way towards minimally invasive MRD assessment in MM pts on maintenance or observation.

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León: Current Employment. **Bladé:** *Janssen:* Other: Honoraria for lectures; *Celgene/Bristol Myers Squibb:* Other: Honoraria for lectures; *Amgen:* Other: Honoraria for lectures; *Sanofi:* Other: Honoraria for lectures. **San-Miguel:** *MSD:* Other: Advisory Board; *Karyopharm:* Other: Advisory Board; *Janssen-Cilag:* Other: Advisory Board; *Haemalogix:* Other: Advisory Board; *GSK:* Other: Advisory Board; *Celgene:* Other: Advisory Board; *BMS:* Other: Advisory Board; *Amgen:* Consultancy, Other: Advisory Board; *Abbvie:* Consultancy, Other: Advisory Board; *Novartis:* Other; *Takeda:* Other: Advisory Board; *Regeneron:* Other: Advisory Board; *Roche:* Other: Advisory Board; *Sanofi:* Other: Advisory Board; *SecuraBio:* Other: Advisory Board. **Puig:** *Amgen:* Consultancy, Honoraria, Other, Research Funding; *BMS:* Consultancy, Honoraria, Other, Research Funding, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Other, Research Funding; *Takeda:* Consultancy, Honoraria, Other, Research Funding; *The Binding Site:* Consultancy, Honoraria; *Sanofi:* Consultancy, Honoraria; *Pfizer:* Research Funding. **Paiva:** *Janssen:* Consultancy, Honoraria; *Gilead:* Honoraria; *Sanofi:* Consultancy, Honoraria, Research Funding; *Oncopeptides:* Honoraria; *Amgen:* Honoraria; *EngMab:* Research Funding; *Roche Glycart AG:* Honoraria, Research Funding; *Bristol-Myers Squibb:* Consultancy, Honoraria, Research Funding; *Takeda:* Honoraria, Research Funding; *GSK:* Honoraria, Research Funding; *Adaptive:* Honoraria.

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