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POSTER ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Sustained Recovery of Uninvolved Heavy/Light Chain Pair Immunoparesis during Maintenance Discriminates Patients with Sustained Negative Minimal Residual Disease

Sunil Lakhwani[1,2], *Laura Rosiñol, MD PhD*[3], *Noemi Puig, MDPhD*[4], *Miguel Angel Pico Picos, MD*[5], *Laura Medina-González, MD*[5], *Joaquin Martinez Lopez, PhD MD*[6], *Bruno Paiva*[7], *Maria Teresa Cedena Romero, MD PhD*[8], *Albert Oriol*[9], *Rafael Ríos, MD PhD*[10], *María Jesús Blanchard, MD*[11], *Isidro Jarque*[12], *Joan Bargay*[13], *Jose Maria Moraleda, MD PhD*[14], *Estrella Carrillo-Cruz, MD*[15], *Anna Maria Sureda Balari, MD PhD*[16], *Isabel Krsnik*[17], *Esther Gonzalez Garcia, MD*[18], *Luis Felipe Casado Montero, MD*[19], *Josep Maria Marti Tutusaus*[20], *Cristina Encinas Rodriguez*[21], *Felipe De Arriba, MD PhD*[22], *Luis Palomera, MD PhD*[23], *Antonia Sampol Mayol*[24], *Yolanda González-Montes, MD*[25], *Cristina Motlló*[26], *Javier De la Cruz, MD*[27], *Rafael Alonso Fernández, MD*[28], *Maria-Victoria Mateos*[29], *Joan Blade Creixenti*[30], *Juan Jose Lahuerta Palacios*[8], *Jesus San Miguel*[7], *Miguel Teodoro Hernández Garcia, MD PhD*[2,5]

[1] Hospital Universitario de Canarias, Sta.Cruz Tenerife, Spain
[2] Universidad de La Laguna, Tenerife, Spain
[3] Amyloidosis and Multiple Myeloma Unit, Department of Hematology, IDIBAPS, Hospital Clinic, Barcelona, Spain
[4] Hospital Universitario de Salamanca (HUSAL), IBSAL, IBMCC (USAL-CSIC), CIBERONC, Salamanca, Spain
[5] Hospital Universitario de Canarias, Tenerife, Spain
[6] Hospital Universitario 12 de Octubre, Madrid, Spain
[7] 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
[8] Hospital Universitario 12 de Octubre, CIBER-ONC CB16/12/00369, CNIO, Madrid, Spain
[9] Catalan Institute of Oncology and Josep Carreras Institute, Hospital Germans Trias i Pujol, Badalona, Spain
[10] Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain
[11] Hospital Universitario Ramon y Cajal, Madrid, Spain
[12] Hospital Universitario La Fe, Valencia, Spain
[13] Hospital Universitario Son Llàtzer. IdIsBa., Palma de Mallorca, Spain
[14] Hospital Clínico Universitario Virgen de la Arrixaca. IMIB-Pascual Parrilla. University of Murcia, Murcia, Spain
[15] Hospital Vírgen del Rocío, Seville, Spain
[16] Institut Catala D'Oncologia, Barcelona, Spain
[17] Hospital Puerta de Hierro, Madrid, Spain
[18] University Hospital Cabueñes, Gijón, Spain
[19] Hospital General Universitario de Toledo, Toledo, Spain
[20] Hospital Universitari Mútua de Terrassa, Terrassa, Spain
[21] Hospital General Universitario Gregorio Marañón, IiSGM, Madrid, Spain
[22] Hospital Morales Meseguer, IMIB-Arrixaca, Universidad de Murcia, Murcia, Spain
[23] Hospital Clinico Universitario Lozano Blesa, Instituto Investigacion Sanitaria Aragon, Zaragoza, Spain
[24] Hospital Universitario Son Espases, Palma de Mallorca, Spain
[25] Institut d'Oncologia Dr. Josep Trueta, Girona, Spain
[26] Hospital Althaia, Xarxa Assistencial de Manresa,, Manresa, Spain
[27] Hospital Universitario 12 De Octubre, Instituto De Investigación Sanitaria,, Madrid, Spain
[28] Department of Hematology, Hospital Universitario 12 de Octubre, Madrid, Spain
[29] University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain
[30] Amyloidosis and Myeloma Unit, Department of Hematology, Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain

Introduction. Immunoparesis (IP) or the suppression of uninvolved immunoglobulins (Ig) is a very common finding in multiple myeloma (MM) patients at diagnosis that confers worse prognosis. In addition to classic total Ig, IP can be measured by the

uninvolved heavy/light chain pair of the same immunoglobulin (uHLC). Previously, we have reported that recovery of uHLC IP in a single time point (at first year of maintenance) is an independent prognostic factor in newly diagnosed MM transplant eligible (NDMM-TE) patients with intensive treatment within a clinical trial, without significant prognostic value for recovery from classic IP in that setting. Moreover, recovery of uHLC IP affords complementary information to single time point minimal residual disease (MRD) for risk stratification. Although, negative sustained MRD is the most important evolutive favorable prognostic factor in MM, some patients relapse despite achieving negative sustained MRD.

Aim. To evaluate the prognostic value of sustained uHLC IP recovery during maintenance treatment, measured by progression free survival (PFS), within a clinical trial of NDMM TE patients with intensive treatment and its potential association with sustained MRD.

Patients & Methods. Patients with newly diagnosed MM enrolled in the PETHEMA/GEM2012MENOS65 trial received six cycle VRD-GEM induction, autologous hematopoietic stem cell transplantation conditioned by melphalan or busulfan plus melphalan and consolidation with two more cycles of VRD-GEM. Afterwards, patients were enrolled in the PETHEMA/GEM2014MAIN clinical trial that randomly assigned them to maintenance with lenalidomide and low-dose dexamethasone (Rd) or Rd plus ixazomib for two years. After two years, patients who achieved negative MRD stopped the treatment and patients who did not achieve MRD negativity received three more years of Rd. We analyzed uHLC in a central laboratory at diagnosis and at the first and second year of maintenance. We consider IP at diagnosis when uHLC were under lower limit of normality (LLN) and recover IP when suppressed uHLC at diagnosis reach at least LLN plus 10%. Sustained uHLC IP recovery was defined as IP recovery in the first year of maintenance that persists in the second year of maintenance. MRD was analyzed by next generation flow cytometry (sensitivity level $2x10^{-6}$) after consolidation and at the first and second year of maintenance. Sustained MRD was defined as a negative MRD for at least 12 months that remains negative at the second year of maintenance.

In the PETHEMA/GEM2012MENOS65 trial, 458 patients were included of which 332 patients entered the PETHEMA/GEM2014MAIN clinical trial. We included in this study 137 patients, those who reached the second year of maintenance without relapse and had samples available at any of the three time points for the uHLC analysis.

Results. We found uHLC IP in 93.7% of patients (119/127) at diagnosis, 28.1% of patients (34/121) at first year of maintenance and 46.8% of patients (51/109) at second year of maintenance. After the second year of maintenance, we found recovery from uHLC IP present at diagnosis in 48.4% of patients (46/95). Patients that recovered from uHLC IP after second year of maintenance had better PFS (p=0.015) with hazard ratio (HR) 0.27 (CI95% 0.09 - 0.84). Patients with sustained recovery from uHLC IP had better prognosis than patients without recovery at first year of maintenance [p=0.010; HR 0.16 (CI95% 0.03 - 0.78)] and patients with IP recovery at first year who lose it at second year of maintenance [p=0.002: HR 0.12 (CI95% 0.02 - 0.59)] (*Figure 1*). Only five patients without recovery at first year had uHLC IP recovery at second year of maintenance, but with similar PFS than patients without recovery at both time points (p=0.441).

Sustained negative MRD for at least 12 months was present in 87/136 (64%) of patients, however we had data of IP recovery evolution in only 54 of these patients, of which 28 had sustained IP recovery. Patients with sustained negative MRD and sustained IP recovery had longer PFS than patients with sustained negative MRD without sustained IP recovery [p=0.025; HR 0.13 (CI95% 0.02 - 0.98)] (*Figure 2*).

Conclusions. Sustained recovery of uHLC IP during maintenance in NDMM-TE patients with intensive treatment is a prognostic factor complementary to sustained negative MRD. Combination of both factors identify patients with very good prognosis.

Disclosures Lakhwani: *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Honoraria; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Rosiñol:** *Amgen:* Other: Honoraria for lectures; *Sanofi:* Other: Honoraria for lectures; *Takeda:* Other: Honoraria for lectures; *GlaxoSmithKline:* Other: Honoraria for lectures; *Bristol Myers Squibb/Celgene:* Other: Honoraria for lectures; *Janssen:* Other: Honoraria for lectures. **Puig:** *Janssen:* Consultancy, Honoraria, Other, Research Funding; *Pfizer:* Research Funding; *BMS:* Consultancy, Honoraria, Other, Research Funding, Speakers Bureau; *Amgen:* Consultancy, Honoraria, Other, Research Funding; *The Binding Site:* Consultancy, Honoraria; *Sanofi:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria, Other, Research Funding. **Martinez Lopez:** *BMS:* Membership on an entity's Board of Directors or advisory committees, Other: Travel grants, Research Funding; *Incyte:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Pfizer:* Membership on an entity's Board of Directors or advisory committees, Other: Travel grants, Research Funding; *Sanofi:* Membership on an entity's Board of Directors or advisory committees, Other: Travel grants, Research Funding; *Janssen:* Membership on an entity's Board of Directors or advisory committees, Other: Travel grants, Research Funding. **Paiva:** *EngMab:* Research Funding; *GSK:* Honoraria, Research Funding; *Takeda:* Honoraria, Research Funding; *Adaptive:* Honoraria; *Sanofi:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria; *Roche Glycart AG:* Honoraria, Research Funding; *Bristol-Myers Squibb:* Consultancy, Honoraria, Research Funding; *Amgen:* Honoraria; *Gilead:* Honoraria; *Oncopeptides:* Honoraria. **Oriol:** *BMS/Celgene:* Consultancy, Honoraria, Speakers Bureau; *GSK:* Consultancy, Honoraria, Speakers Bureau; *Amgen:* Consultancy, Other: Consulting fees. **Jarque:** *Amgen:* Consultancy, Research Funding; *Regeneron Pharmaceuticals, Inc.:* Research Funding; *Janssen:* Honoraria, Research Funding; *Incyte:* Honoraria, Research Funding; *Beigene:* Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding; *Sobi:* Consultancy, Honoraria, Research Funding; *Pfizer:* Consultancy; *Novartis:* Consultancy; *Kyowa Kirin:* Consultancy; *AstraZeneca:* Consultancy, Honoraria, Research Funding. **Moraleda:** *Gilead-Kite:* Honoraria; *Novartis:* Speakers Bureau; *BMS/Celgene:* Speakers Bureau; *Roche:* Speakers Bureau; *Jazz Pharma:* Other: Advisory board. **Sureda Balari:** *Astra Zeneca:* Consultancy, Honoraria; *Sanofi:* Consultancy, Honoraria; *MSD:* Consultancy, Honoraria; *BMS/Celgene:* Consultancy,

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Figure 1. PFS according to evolution of uHLC IP recovery at first and second year of maintenance.

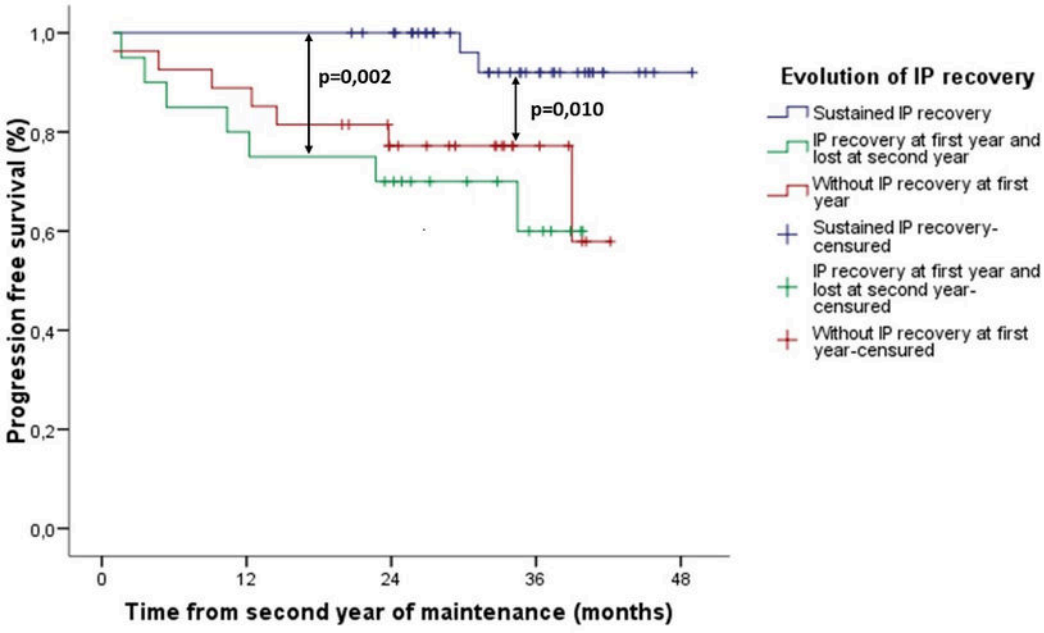

Figure 2. PFS according to sustained uHLC IP recovery status in sustained negative MRD patients.

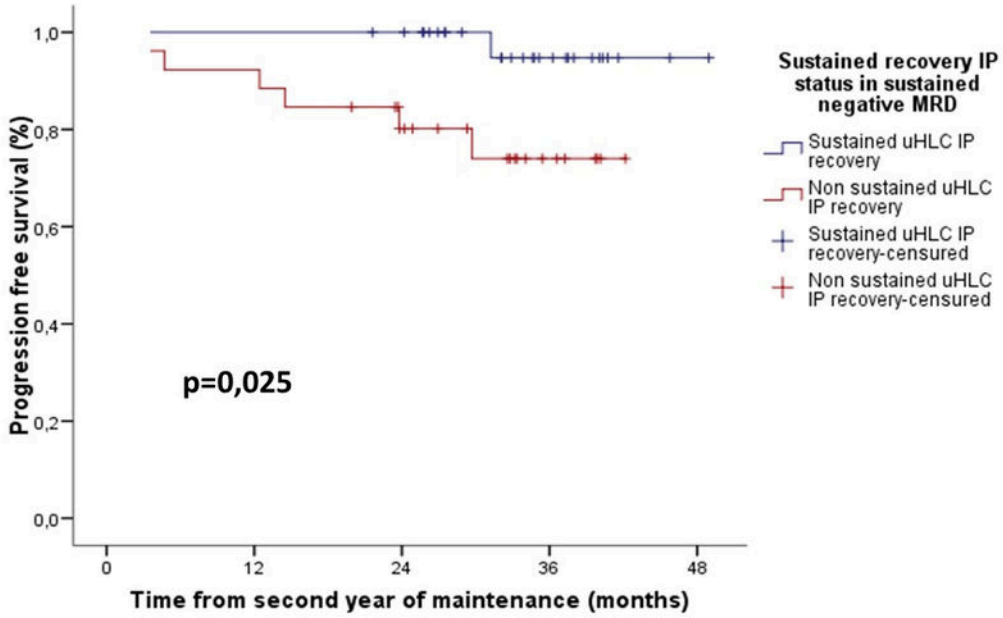

Figure 1

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