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TO THE EDITOR:

Validation of the International Myeloma Working Group standard response criteria in the PETHEMA/GEM2012MENOS65 study: are these times of change?

Ana Jiménez-Ubieto,[1,*] Bruno Paiva,[2,*] Noemi Puig,[3] Maria-Teresa Cedena,[1] Joaquín Martínez-López,[1] Albert Oriol,[4] María-Jesús Blanchard,[5] Rafael Ríos,[6] Jesús Martin,[7] Rafael Martínez,[8] Anna Sureda,[9] Miguel-Teodoro Hernández,[10] Javier de la Rubia,[11] Isabel Krnisk,[12] Valentín Cabañas,[13] Luis Palomera,[14] José María Sánchez-Pina,[1] Joan Bargay,[15] María-Victoria Mateos,[3] Laura Rosiñol,[16] Joan Blade,[16] Jesús San Miguel,[2,†] and Juan José Lahuerta[1,†] on behalf of the GEM (Grupo Español de Mieloma)/PETHEMA (Programa Español de Tratamientos en Hematología) Cooperative Study Group

[1]Centro de Investigación Biomédica en Red de Cáncer (CIBERONC) CB16/12/00369, Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Clínica Universidad de Navarra, Centro de Información de Medicamentos (CIMA), Instituto de Investigación Sanitaria de Navarra (IDISNA), CIBERONC CB16/12/00369, Pamplona, Spain; [3]Hospital Universitario de Salamanca (IBSAL), Instituto de Biología Molecular y Celular del Cáncer (IBMCC)–Centro de Investigación del Cancer (CSIC), Salamanca, Spain; [4]Hospital Germans i Trials, Barcelona, Spain; [5]Hematology Department, Hospital Ramón y Cajal, Madrid, Spain; [6]Hospital Universitario Virgen de las Nieves de Granada, Granada, Spain; [7]Hospital Universitario Virgen del Rocío, Sevilla, Spain; [8]Hospital Clínico San Carlos, Madrid, Spain; [9]Institut Catalá d'Oncologia-l'-Hospitalet, Instituto de Investigació Biomèdica de Bellvitge (IDIBELL), Universitat de Barcelona, Barcelona, Spain; [10]Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain; [11]Hospital La Fe, Valencia, Spain; [12]Hospital Puerta de Hierro, Madrid, Spain; [13]Hospital Virgen de la Arrixaca, El Palmar, Spain; [14]Hospital Clínico Universitario Lozano Blesa, Ils Aragón, Zaragoza, Spain; [15]Hospital Son Llatzer, Palma de Mallorca, Spain; [16]Hospital Clinic, Institut d'Investigacions Biomédiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain

Induction and consolidation based on proteasome inhibitors, immunomodulatory drugs, and corticoids integrated with high-dose therapy (HDT) and autologous stem cell transplantation (ASCT), are showing complete response (CR) rates >50% in multiple myeloma (MM).[1-3] The addition of anti-CD38 monoclonal antibodies may increase these unprecedented CR rates.[4-6] When more than half of transplant-eligible patients with MM achieve CR with frontline therapy, it is reasonable to ask, what other tests are clinically relevant after negative immunofixation.

The achievement of deep responses with modern therapy led the International Myeloma Working Group (IMWG) to propose new guidelines that included definitions of negative minimal residual disease (MRD) for standard response criteria.[7] Indeed, recent studies have reported nearly 50% MRD$^-$ rates,[5,8,9] and, more importantly, the prognostic value of MRD criteria was validated in clinical trials[8,10-12] and routine practice.[13,14] However, the clinical significance of standard response criteria in patients who are MRD positive has not been investigated in current treatment scenarios.

Four hundred forty-nine newly diagnosed, transplant-eligible patients enrolled in the phase 3 PETHEMA/GEM2012MENOS65 trial (registered on clinicaltrials.gov, as NCT01916252) and with available response assessment, were included in this study.[1] Afterward, patients were enrolled in the PETHEMA/GEM2014MAIN trial (NCT02406144).[8] Patients' demographics and clinical features have been described elsewhere.[1] Minimal Residual Disease (MRD) was assessed using next-generation flow (NGF) cytometry, as reported recently.[8] An independent ethics committee approved the protocol, and informed consent forms were required before patients were enrolled. Studies were conducted per the ethical principles of the Declaration of Helsinki.

Response was assessed after the last induction cycle, at day 100 after HDT/ASCT, and after the second consolidation course. Seventy-four patients were not evaluated after consolidation. Response was defined per the 2016 guidelines[7] with 2 exceptions: (1) patients with ≤5% bone marrow plasma cells (BMPCs) and negative serum immunofixation, but unavailable urine immunofixation data, were reclassified as attaining CR according to our recent findings indicating identical outcomes[15]; (2) patients showing $<2 \times 10^{-6}$ tumor cells were defined as having undetectable MRD, regardless of the depth of serological response, because the outcomes were identical between those with persistent and absent M-component.[8] Differences were tested for statistical significance with the (2-sided) log-rank test, and hazards ratios (with its 2-sided 95% confidence interval) were estimated with a Cox regression model.

We started by analyzing the prognostic value of standard response criteria after 6 induction cycles with bortezomib, lenalidomide, and dexamethasone (VRD); HDT/ASCT; and consolidation with 2 VRD courses. With a median follow-up of 5 years, achieving CR or stringent CR (sCR) after induction resulted in significantly superior progression-free survival (PFS) when compared with very good partial response (VGPR) or PR (Figure 1A). After HDT/ASCT, patients in CR or sCR continued showing more prolonged PFS compared with those in VGPR,

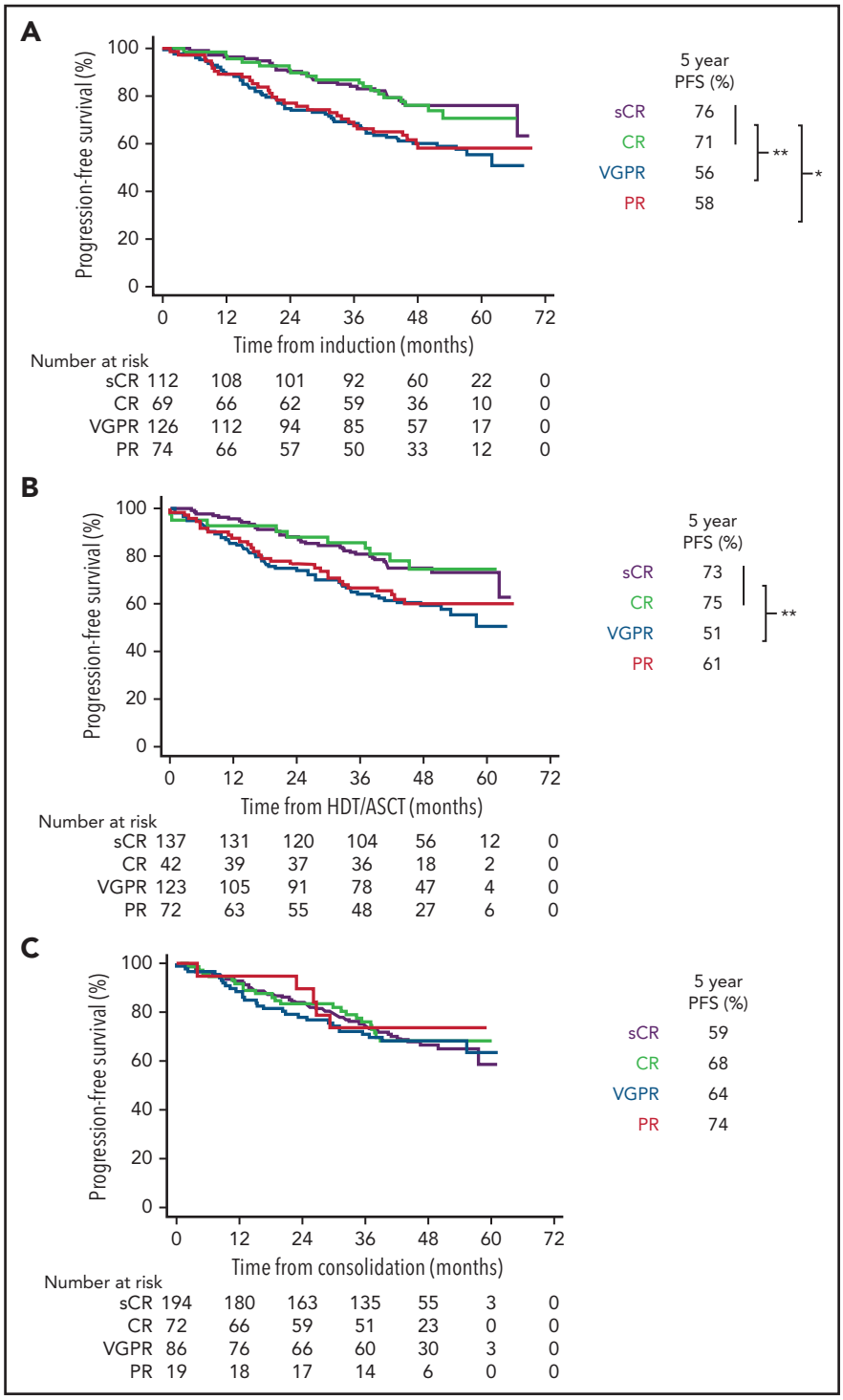

Figure 1. Depth of response based on standard response criteria. PFS of patients achieving sCR, CR, VGPR, and PR after 6 induction cycles of VRD (A); ASCT conditioned with Bu-Mel or Mel-200 HDT (B); or 2 consolidation cycles of VRD (C). PFS was defined as time from response assessment until disease progression or death from any cause and was estimated by the Kaplan-Meier method. OS was defined as time from response assessment until death from any cause. *$P < .05$; **$P < .01$; ***$P < .001$.

though not those in PR (Figure 1B). Surprisingly, the differences disappeared after consolidation (Figure 1C). Less than half of the patients in VGPR (39 of 86; 45%) and in PR (6 of 19; 32%) after consolidation have respectively achieved CR/sCR during the first year of maintenance, excluding deepening of response at later stages as a unifying reason to explain similar PFS between these patients and those in CR or sCR after consolidation. These data urge further investigations to understand the limitations of standard response criteria.

In 1998, a cutoff of <5% BMPCs by conventional cytology was added into the CR criteria.[16] Thus, we investigated whether it remains informative >20 years later. The median percentage of PCs by morphology was 1.7% (range, 0-5) in the 266 patients in

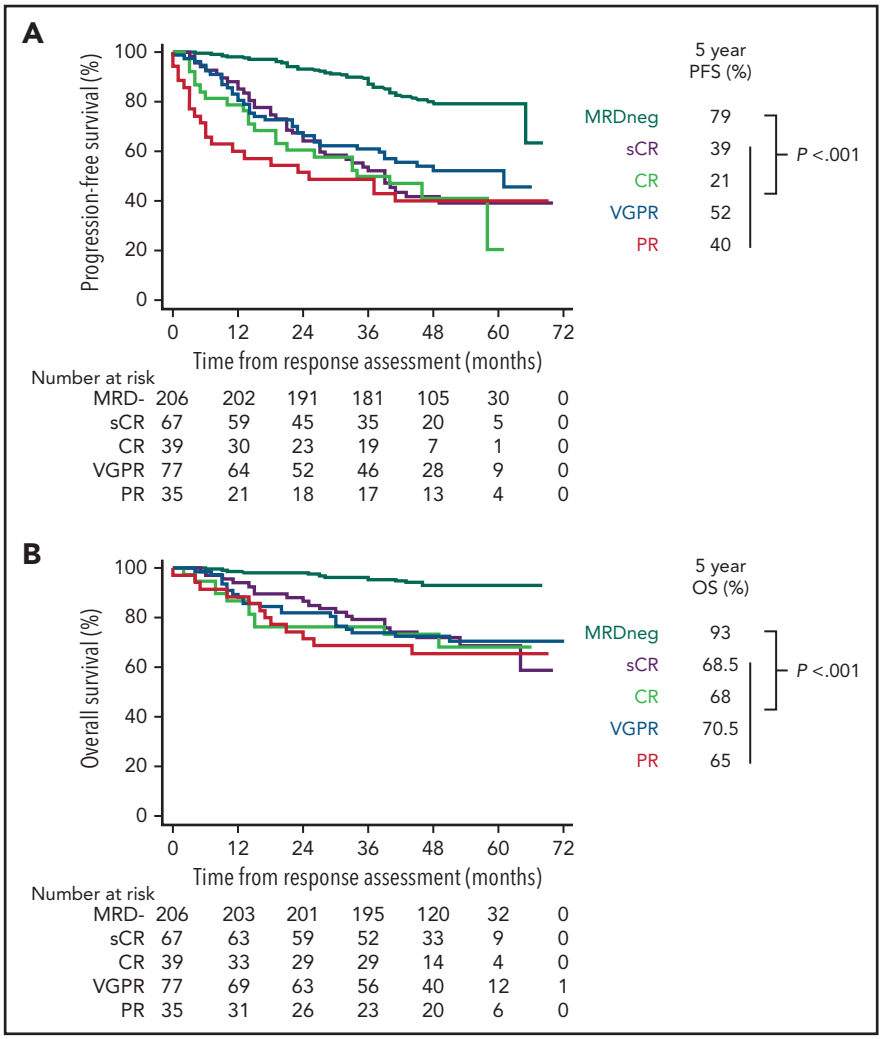

Figure 2. Depth of response based on standard and MRD response criteria. PFS (A) and OS (B) of patients stratified according to best response achieved during treatment: MRD$^-$, sCR, CR, VGPR, and PR. There were no significant differences in PFS and OS in the comparison of patients achieving sCR, CR, VGPR or PR. PFS was defined as time from best response achieved until disease progression or death from any cause and was estimated by the Kaplan-Meier method. OS was defined as time from best response achieved until death from any cause.

CR or sCR after consolidation, and PC enumeration by morphology had no prognostic value (data not shown). Of note, only 4 of 270 (1.5%) patients with a negative immunofixation had >5% BMPCs and therefore, were not classified as being in CR at that time point (all 4 cases achieved CR later on; 1 had progressive disease and died, whereas the others remained progression free). This percentage is almost 10-fold inferior to that reported >10 years ago by Chee et al[17] and stresses the limited value of cytological response assessment in transplant-eligible patients, with patients with MM reaching high-quality remission with novel drug combinations.

BM biopsies were first introduced in the 2006 response criteria[18] to evaluate PC clonality using immunohistochemistry or immunofluorescence. Namely, it required the analysis of a minimum of 100 PCs and a κ/λ ratio of >4:1 or <1:2 in patients with MM with the κ or λ isotype. Accordingly, clonality was respectively defined whenever >80% total PCs stained for κ or >50% total PCs stained for λ. We found that the median percentage of clonal and normal PCs among total PCs identified by NGF in patients achieving CR or sCR after consolidation was 3% and 97%, respectively (supplemental Figure 1A). These findings uncover that the median percentage of normal PCs is 32-fold greater than that of clonal PCs within the PC compartment and expose that simple κ/λ ratios measured in 100 PCs[7] do not detect such low levels of residual disease. Indeed, the median level of MRD was 0.03% (range, 0.0002% to 0.59%; supplemental Figure 1B) and only 1% of patients with κ and 3% of patients with λ MM, respectively, had >80% and >50% clonal PCs of the total PCs.

The serum free light-chain (sFLC) ratio was introduced alongside BM clonality, as previously defined, to create the sCR criteria.[18] We found that almost one-fourth of patients in CR after consolidation display an abnormal sFLC ratio (72 of 266; 27%), but their PFS was identical with that of cases with a normal sFLC ratio (Figure 1C). Similar results were observed after induction and HDT/ASCT (Figure 1A-B). Altogether, these data raise questions about the sensitivity and clinical utility of immunohistochemistry and immunofluorescence and the sFLC assays in patients in CR treated with optimal intensive treatment. As a result, the superiority of sCR

criteria over standard CR criteria could not be confirmed in this study or elsewhere.[19]

We had shown with low-sensitivity flow cytometry that MRD was detected in approximately one-third of patients in CR who had been treated with older regimens.[20-22] In this study, NGF enabled the detection of MRD in 73 of 252 (29%) patients in CR or sCR after consolidation and, in most cases, MRD levels ranged between 10^{-6} and 10^{-5} (58 of 73; 79%). These results endorse the IMWG 2016 response assessment guidelines that indicate a minimum sensitivity of 10^{-5},[7] given that MRD criteria based on a threshold of 10^{-4} would have limited value in patients achieving high-quality remission induced by newer, more effective regimens. Accordingly, there were significant differences in PFS and OS (supplemental Figure 2) among patients in CR or sCR who had positive vs negative MRD, which further validates the inclusion of the former in the 2016 response criteria. Of note, transplant-eligible patients in CR or sCR with positive MRD after induction and consolidation with VRD showed a median PFS of 3 years. These findings further support that MRD negativity and not CR should be the new end point in transplant-eligible MM, although questions about the timing, periodicity, and sensitivity of MRD assessment remain unresolved.

Although the prognostic value of CR and sCR is limited when compared with that of MRD, it could be that standard response criteria are of prognostic value in patients who remain MRD^+. However, we found no significant differences in PFS ($P \geq .089$; Figure 2A) and OS ($P \geq .496$; Figure 2B) across patients with persistent MRD, regardless of the achievement of sCR, CR, VGPR, or even PR. PFS rates at 5 years were 43%, 35%, 51%, and 40%, respectively; similar results were observed for OS (75%, 73.5%, 68%, and 66% at 5 years). These numbers were significantly inferior to those of patients achieving undetectable MRD (5-year PFS and OS of 79% and 93%, respectively). Thus, our results reproduce and expand previous observations of modern therapies, wherein attaining CR or sCR without MRD clearance is no better than a VGPR or PR in terms of PFS and OS.[20] Of further note, patients in sCR, CR, or VGPR showed similar survival upon achieving undetectable MRD (supplemental Figure 3). Thus, and with the possible exception of patients with extramedullary disease and elevated LDH levels,[8] undetectable MRD in cases of persistent M-component should not be generalized as a false-negative result.

The clinical value of serial measurements of the M-protein and sFLC during patient treatment and follow-up is undeniable. Our findings merely exposed the limited utility of standard response criteria to predict different PFS in transplant-eligible MM treated with VRD induction and consolidation. In nontransplant candidates treated with less intensive regimens, such as that of the PETHEMA/GEM CLARIDEX trial, we observed that patients achieving sCR or CR and VGPR had similar outcomes, whereas those in PR displayed inferior PFS (supplemental Figure 4). Consequently, our results urge other groups to investigate these findings in this and other treatment scenarios. If reproducible, such data could support a new iteration of the IMWG 2016 guidelines for response assessment, which may reflect the direct usage of BM aspirates for MRD testing, the standardization of positron emission tomography/computed tomography,[23] and the incorporation of novel methods such as mass spectrometry to measure serological response in MM.[9,24,25]

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Authorship

Contribution: A.J.-U., B.P., J.S.M., and J.J.L. conceived the analysis; A.J.-U., B.P., M.-V.M., L.R., J. Blade, J.S.M., and J.J.L. designed the analysis protocol; B.P., M.-T.C., and N.P. analyzed the flow cytometry data; A.J.-U., B.P., J.S.M., and J.J.L., analyzed and interpreted the data; A.J.-U. and B.P. performed the statistical analysis; A.J.-U., B.P., J.S.M., and J.J.L. wrote the manuscript; and all authors provided study material or patients and reviewed and approved the manuscript.

Conflict-of-interest disclosure: B.P. reports receiving honoraria for lectures from and membership on advisory boards with Adaptive, Amgen, Bristol-Myers Squibb-Celgene, Creative BioLabs, Janssen, Kite Pharma, Sanofi and Takeda; unrestricted grants from Celgene, EngMab, Roche, Sanofi, and Takeda; and consultancy for Bristol-Myers Squibb-Celgene, Janssen, Sanofi and Takeda. N.P. has received honoraria from Janssen-Cilag, Takeda, and Amgen, and has served in a consulting or advisory role and received travel, accommodations, and expenses from Janssen-Cilag. A.O. has served in a consulting or advisory role for Amgen and Janssen-Cilag. A.S. has received honoraria from Takeda, MSD, BMS/Celgene, Janssen, Amgen, Novartis, Gilead-Kite, Sanofi, Roche, and Alexion; has served in a consulting or advisory role for Takeda, BMS/Celgene, Novartis, Janssen, Gilead Kite, and Sanofi; and has served on the speakers' bureau for Takeda. L.P. has received honoraria from and served in a consulting or advisory role for Janssen-Cilag and Celgene. M.-V.M. has received honoraria from and has served on the speakers' bureau for Janssen-Cilag and Celgene. L.R. has received honoraria from Janssen-Cilag and Celgene. J. Blade has received honoraria for lectures and advisory boards from Janssen-Cilag, Celgene, Amgen, and Takeda. J.S.M. has served as a consultant for Bristol-Myers Squibb, Janssen-Cilag, Celgene, Merck, Takeda, Novartis, Amgen, Sanofi, and Roche. J.J.L. has received honoraria for lectures from and has participated in advisory boards for Janssen-Cilag, Celgene, Takeda, Amgen, GSK, and Sanofi. The remaining authors declare no competing financial interests.

A complete list of the members of the GEM/PETHEMA Cooperative Study Group appears in the supplemental appendix.

ORCID profiles: B.P., 0000-0003-1977-3815; N.P., 0000-0001-7535-3861; M.-T.C., 0000-0001-5851-3720; J.M.-L., 0000-0001-7908-0063; A.O., 0000-0001-6804-2221; M.-T.H., 0000-0002-6576-7881; J.d.l.R., 0000-0002-8354-768X; I.K., 0000-0002-2912-5072; V.C., 0000-0002-6248-2549; J.S.-P., 0000-0002-9181-0900; M.-V.M., 0000-0003-2390-1218; L.R., 0000-0002-2534-9239; J.S.M., 0000-0002-9183-4857; J.J. éL., 0000-0002-3393-9570.

Correspondence: Juan José Lahuerta, Instituto de Investigación Sanitaria Hospital Universitario 12 de Octubre, Avenida de Córdoba s/n. 28041, Madrid, Spain; e-mail: jjlahuerta@telefonica.net.

Footnotes

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*A.J-U. and B.P. contributed equally to this study as first authors.

†J.S.M. and J.J.L. contributed equally to this study as last authors.

Requests for original data should be directed to the corresponding author (jjlahuerta@telefonica.net).

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