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Depth of Response in Multiple Myeloma: A Pooled Analysis of Three PETHEMA/GEM Clinical Trials

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Depth of Response in Multiple Myeloma: A Pooled Analysis of Three PETHEMA/GEM Clinical Trials

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Abstract

Purpose—To perform a critical analysis on the impact of depth of response in newly diagnosed multiple myeloma (MM).

Patients and Methods—Data were analyzed from 609 patients who were enrolled in the GEM (Grupo Español de Mieloma) 2000 and GEM2005MENOS65 studies for transplant-eligible MM and the GEM2010MAS65 clinical trial for elderly patients with MM who had minimal residual disease (MRD) assessments 9 months after study enrollment. Median follow-up of the series was 71 months.

Results—Achievement of complete remission (CR) in the absence of MRD negativity was not associated with prolonged progression-free survival (PFS) and overall survival (OS) compared with near-CR or partial response (median PFS, 27, 27, and 29 months, respectively; median OS, 59, 64, and 65 months, respectively). MRD-negative status was strongly associated with prolonged PFS (median, 63 months; $P < .001$) and OS (median not reached; $P < .001$) overall and in subgroups defined by prior transplantation, disease stage, and cytogenetics, with prognostic superiority of MRD negativity versus CR particularly evident in patients with high-risk cytogenetics. Accordingly, Harrell C statistics showed higher discrimination for both PFS and OS in Cox models that included MRD (as opposed to CR) for response assessment. Superior MRD-negative rates after different induction regimens anticipated prolonged PFS. Among 34 MRD-negative patients with MM and a phenotypic pattern of bone marrow involvement similar to monoclonal gammopathy of undetermined significance at diagnosis, the probability of “operational cure” was high; median PFS was 12 years, and the 10-year OS rate was 94%.

Conclusion—Our results demonstrate that MRD-negative status surpasses the prognostic value of CR achievement for PFS and OS across the disease spectrum, regardless of the type of treatment or patient risk group. MRD negativity should be considered as one of the most relevant end points for transplant-eligible and elderly fit patients with MM.

Introduction

The multiple myeloma (MM) treatment landscape has evolved remarkably during the past 15 years, with the introduction of multiple novel drugs significantly improving survival in patients with MM.^{1,2} Progress has also been made in understanding disease biology,³ diagnostic criteria,⁴ and patient stratification.^{5,6} However, response criteria and clinical end points have largely remained the same.^{7–9}

Retrospective analyses among transplant-eligible and nontransplant patients have suggested a link between depth of response (eg, complete remission [CR]) and prolonged survival.^{10,11} However, the clinical relevance of CR and its utility as an end point in MM have been

questioned^{12,13} because CR rates obtained after different treatment regimens do not always predict distinct outcomes^{14–16} and because select patient subgroups, for example, those with monoclonal gammopathy of undetermined significance (MGUS)-like phenotypic profiles or specific molecular subtypes, may experience long-term survival without achieving CR.^{17–20} Furthermore, recent studies have shown CR rates of ~50%,^{21–25} but not all these patients experience long-term survival. It is therefore critical to improve response assessment in MM by incorporating more sensitive methods for detecting minimal residual disease (MRD).

Studies show that MRD status is one of the most relevant independent prognostic factors in MM^{26–28} and that persistence of MRD is consistently a predictor for inferior progression-free survival (PFS).^{21,26–37} Some studies have failed to show a correlation between MRD negativity and prolonged overall survival (OS),^{21,27,30,34,38} but these were mainly conducted in small patient series (particularly in elderly MM) and had relatively short follow-up. Indeed, MRD studies typically include small numbers of patients, precluding subanalyses that could help consolidate the role of MRD as a treatment-independent biomarker,³⁵ a clinically relevant end point for high-risk patients with MM,³⁴ and a surrogate marker for survival.

Patients and Methods

Patients and Treatment

This pooled analysis included 609 newly diagnosed patients with MM enrolled in three clinical trials—GEM (Grupo Español de Mieloma) 2000 (n = 256) and GEM2005MENOS65 (n = 226) for transplant-eligible patients, and GEM2010MAS65 (n = 127) for transplant-ineligible patients. For landmark analyses, patients were required to have MRD assessed at a specific time point, namely, 9 months after study enrollment (ie, after high-dose therapy/autologous stem cell transplantation [HDT/ASCT] or after nine induction cycles in nontransplant candidates). Thus, patients who had died or had progressive disease at the landmark, or had MRD assessments before or after 9 months after study enrollment, were excluded from this analysis (n = 188). Patients included in the GEM2005MAS65 clinical trial were also excluded because MRD was assessed 6 months after study enrollment. To ensure consistency of inclusion criteria for patients in this analysis from across the three different protocols, GEM2000 patients who had nonsecretory MM, were > 70 years of age, had serum creatinine > 2 mg/dL, or had relevant comorbidities were also excluded (n = 39).

The three individual study designs have been described elsewhere^{16,22,39,40} and are illustrated in Fig 1. Patient characteristics are listed in Appendix Table A1 (online only). The study was approved by the Spanish National Health Service and local ethics committees of all participating centers. Each patient gave written informed consent to participate. The study was conducted in accordance with the Declaration of Helsinki. Median follow-up of the whole series was 71 months.

Clinical End Points and Assessments

PFS was measured from time of MRD assessment, per protocol, 9 months after study enrollment to date of progression, relapse, or death. Patients who had not progressed or relapsed were censored on the last date they were known to be alive. OS was calculated from 9 months after study enrollment at the time of MRD assessment to the date of death or last follow-up visit. Disease response was assessed using European Group for Blood and Marrow Transplantation criteria,⁷ modified to include near-CR (nCR; negative electrophoresis, positive immunofixation).³⁹ Per protocol, prespecified bone marrow (BM) aspirates for MRD evaluations were scheduled after induction (both transplant-eligible and transplant-ineligible patients; n = 322) and at day 100 after HDT/ASCT (n = 482). MRD was typically assessed in patients achieving a serologic response; of 609 patients with MRD assessments, 286 (47%), 114 (19%), and 177 (29%) achieved CR, nCR, and partial response (PR), respectively. These patients had significantly superior outcomes versus patients achieving lower-quality responses in whom MRD assessments were not performed or performed outside the landmark analysis (Data Supplement). MRD was investigated in BM samples using either four-color (CD38-FITC/CD56-PE/CD19-PerCPCy5.5/CD45-APC; GEM2000, GEM2005MENOS65) or eight-color (CD45-PacB/CD138-OC515/CD38-FITC/CD56-PE/CD27-PerCPCy5.5/CD19-PECy7/CD117-APC/CD81-APCH7; GEM2010MAS65) antibody combinations; immunopheno-typic strategies for discriminating between normal and clonal plasma cells (PCs) have been described elsewhere.^{26,29,30,41} MRD negativity was defined as < 20 clonal PCs detected by multiparameter flow cytometry after measuring 200,000 nucleated cells, at a sensitivity level of 10⁻⁴ to 10⁻⁵. MRD assessment was centralized in three PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas)/GEM core laboratories.

Assessment of Phenotypic Profiles

An automated algorithm was used to identify patients displaying MGUS-like immunophenotypic profiles.²⁰ Briefly, the relative frequency of BM PCs and percentages of clonal and normal PCs within the whole BM PC compartment were determined at diagnosis in 478 of 609 patients. Principal component analysis (PCA) on the basis of these three variables was performed and graphically visualized by the automated population separator (PCA1 v PCA2) dot-plot representation of Infinicyt software (Cytognos, Salamanca, Spain). 20 Patients plotted outside the MM group (defined by 1.5 standard deviation) and inside the MGUS cluster (defined by 1.5 standard deviation) were classified as MGUS-like and all other cases as MM-like.²⁰

Cytogenetic Characterization

Fluorescent in situ hybridization (FISH) was performed at diagnosis on immunomagnetically enriched PCs from 370 of 609 patients for immunoglobulin heavy-chain translocations, del(13q14), and del(17p13). Patients with t(4;14), t(14;16), and/or del(17p13) were classified as high risk (n = 60); others were classified as standard risk (n = 310).

Statistical Analysis

The χ^2 test was used to estimate the statistical significance of different MRD rates between groups. Landmark survival analyses (from time of response assessment) were plotted per Kaplan-Meier methodology; differences between curves were tested for statistical significance with the (two-sided) log-rank test. Variables with a significant impact on survival in univariable analysis were included in a multivariable Cox proportional hazard model. Variables were retained in the model for levels of significance of $P < .05$. A comparison between Cox models for PFS and OS according to depth of response defined by CR or MRD negativity was performed. Models were adjusted for age, transplant eligibility, International Staging System (ISS) disease stage, lactate dehydrogenase level, and fluorescence in situ hybridization cytogenetics. The Harrell C-statistic, the Akaike information criterion (AIC), and the Bayesian information criterion (BIC) were used to evaluate and compare discrimination and predictive performance of models. Calibration was assessed graphically by comparing observed (Kaplan-Meier method) and predicted survival probabilities. Logistic regression models were performed to determine which variables had independent predictive value for long-term survival (ie, PFS 10 years). Statistical analyses were performed with SPSS software (version 20.0; IBM, Chicago, IL) and Stata (Release 14; StataCorp, College Station, TX).

Results

Depth of Response and Survival: MRD Surpasses CR

Patients who achieved CR ($n = 286$ of 609; 47%) experienced significantly superior PFS (median, 49 months) versus patients achieving nCR, PR, or less than PR (median, 37, 34, and 11 months, respectively; Fig 2A). Patients in CR also showed significantly longer OS (median, 128 months) than those in PR (75 months) or less than PR (28 months), but not nCR (77 months; Fig 2B). That notwithstanding, the survival benefit for patients in CR was specifically due to MRD negativity ($n = 259$; Figs 2C and 2D). In fact, only MRD negativity conferred significant prolongation in PFS and OS (medians, 63 and not reached, respectively), because MRD-positive patients in CR had similar survival to MRD-positive patients in nCR and PR (median, PFS, 27, 27 and 29 months, respectively; median OS, 59, 64, and 65 months, respectively). Patients who were MRD-negative despite a persistent M-component showed similar PFS and OS to patients with MRD-negative disease in CR (Data Supplement).

Impact of Depth of Response Across Transplant-Eligible and Ineligible Patients, Disease Stage, and Cytogenetics: Multivariable Analyses

The benefit of achieving CR versus MRD was analyzed among transplant-eligible and transplant-ineligible patients, and in subgroups stratified according to disease stage and cytogenetics. MRD negativity surpassed CR in terms of reduced risk of progression and/or death (overall PFS hazard ratio [HR], 0.42, and OS HR, 0.33, for MRD negativity; overall PFS HR, 0.67, and OS HR, 0.58, for CR), in both transplant-eligible and ineligible patients, in ISS disease stage I, II, and III, as well as in standard- and high-risk cytogenetics subgroups (Figs 3A-3D).

In patients with MRD-negative response, PFS was not significantly different between transplant-ineligible patients (n = 40) and those who underwent transplantation (n = 219; median PFS, 65 v 63 months; $P = .91$) or between patients ≥ 65 years of age (n = 52) and < 65 years (n = 207; median PFS, 62 v 63 months; $P = .30$; Data Supplement). PFS was not significantly different between MRD-negative patients with ISS disease stage III versus II or I ($P = .34$ for both comparisons; Data Supplement).

Although achievement of CR had no significant impact on the outcome of patients with high-risk cytogenetics, MRD-negative patients with high-risk cytogenetics (n = 25) had prolonged PFS (median, 38 v 14 months; $P < .001$) and superior OS (median, 128 v 26 months; $P < .001$) versus patients who were MRD-positive (n = 35; Data Supplement). The dismal outcome of patients who were MRD-positive with high-risk cytogenetics was also observed among patients in CR (9 of 10 progressed, 7 of 10 died), confirming the relationship between these two adverse features and unsustained CR. Conversely, MRD negativity was consistently associated with improved PFS and OS among patients in CR regardless of prior transplant, disease stage, or cytogenetics (Data Supplement).

Multivariable analyses showed that only fluorescent in situ hybridization cytogenetics and MRD status had independent prognostic value for PFS and OS; age, transplant eligibility, and disease stage were independent prognostic markers for OS (Appendix Table A2). Accordingly, CR status did not show independent prognostic value for PFS and OS. Comparison of Cox models for PFS and OS, adjusted for baseline variables and according to CR or MRD status, confirmed the superiority of MRD status across all statistical tests (Table 1). The Harrell C-statistics showed higher discrimination for both PFS and OS in Cox models that included MRD (as opposed to CR) for response assessment; these models also showed lower AIC and BIC. Graphical comparisons between observed and predicted survival probabilities of models including CR or MRD showed accurate calibration for both PFS and OS (Data Supplement).

MRD to Evaluate Treatment Efficacy After Induction and HST/ASCT

Rates of MRD negativity after different induction regimens before HDT/ASCT ranged from 11% with vincristine, carmustine, cyclophosphamide, prednisone/vincristine, carmustine, doxorubicin, and dexamethasone, 17% with thalidomide and dexamethasone, and 31% with vincristine, carmustine, cyclophosphamide, prednisone/vincristine, carmustine, doxorubicin, and dexamethasone/bortezomib, up to 50% with the bortezomib-thalidomide-dexamethasone (VTD) induction regimen. The MRD-negative rate with VTD was significantly superior versus the other regimens (Fig 4A), and despite the effect of subsequent HDT/ASCT and maintenance, it was still associated with trends for prolonged PFS and OS (Figs 4B and 4C).

We then investigated the value of MRD negativity as a clinical end point in this setting by comparing outcomes between patients in CR according to MRD status before and after HDT/ASCT. Median PFS and OS were similar in patients who were MRD-positive before but MRD-negative after HDT/ASCT and in patients who maintained MRD-negative status before and after HDT/ASCT. PFS and OS were inferior among patients who were MRD-positive before and after HDT/ASCT (Figs 4D and 4E).

Clinical Benefit of MRD Negativity in MGUS-Like MM

Taking advantage of the large follow-up of patients enrolled in the GEM2000 study, we sought to define the frequency of, and predictive biomarkers for, operational cure (ie, PFS > 10 years). Two-hundred forty-nine patients in GEM2000 who had either relapsed or died within 10 years after diagnosis (n = 221) or remained progression free and alive for 10 years (n = 28; 11%) were eligible for this subanalysis. Compared with the former, patients with PFS > 10 years more frequently had MGUS-like phenotypic signatures (30% v 8%; $P = .003$) and more commonly achieved MRD negativity (23% v 6%; $P < .001$). Other parameters, including age, anemia, Durie-Salmon Staging System, ISS, lactate dehydrogenase level, DNA ploidy, proliferation index, cytogenetics, and CR achievement, were not significantly different when compared with patients with PFS < 10 years (data not shown). In a larger population of 478 patients from all three clinical trials who had available information on phenotypic profile at diagnosis and MRD status after therapy (the only biomarkers with the significant predictive value for long-term survival), patients with MGUS-like/MRD-negative disease (n = 34) had a median PFS of 12 years and a 10-year OS rate of 94%, which were significantly ($P < .001$) superior to outcomes for patients with MGUS-like/MRD-positive or MM-like/MRD-negative disease (Fig 5).

Discussion

Significant tumor cytoreduction is essential for disease control and eventual cure in hematologic malignancies.^{42–44} Our results confirm that, in MM, depth of response is strongly associated with survival, with greater benefit for patients achieving CR versus nCR (equivalent term to very good PR), suggesting that these populations should not be pooled.⁴⁵ We also showed that the value of CR is intrinsically related to a high proportion of patients who were MRD-negative in this response category; patients who were MRD-positive in CR did not have superior outcomes versus patients who were MRD-positive achieving nCR or PR. On the basis of the remarkable reduction in risk of progression and/or death (PFS HR, 0.42; OS HR, 0.33), as well as on Harrell C-statistics in Cox models adjusted for baseline variables, our results support MRD negativity being considered as one of the most relevant clinical end points and an aim of MM treatment of transplant-eligible and elderly patients who can tolerate intensive therapies.

Ongoing improvements in treatment have resulted in an unmet need for reliable biomarkers to compare effective regimens, reduce the time required to demonstrate survival differences, and, ultimately, accelerate drug approval. Those biomarkers should be universally applicable and reproducible, and have predictive value regardless of treatment and disease biology. Our results demonstrate that patients who were MRD-negative had consistently superior outcomes compared with patients who were MRD-positive in transplant and nontransplant settings, and across disease stage and cytogenetic subgroups. Furthermore, we showed that significantly higher MRD-negative rates after VTD induction (one of the current standards of care in MM) translated into superior survival rates versus other induction regimens before HDT/ASCT. Our results also suggest that MRD monitoring could identify patients in CR who might benefit from HDT/ASCT, as well as a small subset of patients with MRD-positive disease in CR with high-risk cytogenetics who have dismal outcomes and could

benefit from consolidation before maintenance. However, our findings do not establish a role for MRD evaluation in tailoring patients' treatments; this should be investigated in new clinical trials, including assessments of MRD status at additional time points beyond day 100 after HDT/ASCT to optimize treatment duration (particularly post-ASCT consolidation and maintenance therapy). Other outstanding clinical questions include the roles of HDT/ASCT for patients with MRD-negative disease after modern induction therapies, continuous therapy for elderly patients reaching MRD negativity, and the role of MRD with the inclusion of immune therapies. Nonetheless, our results support the adoption of MRD testing in routine practice to help discriminate between patients with clinically meaningful (MRD-negative) and misleading (MRD-positive) CRs.

One limitation of our study is the use of two different flow cytometry methods (eight- and four-color) with different sensitivities (10^{-5} and 10^{-4} , respectively).⁴¹ Flow cytometry is universally applicable for MRD monitoring in MM, and, despite the lack of harmonization in prior studies,^{46,47} its prognostic value has been consistently demonstrated.^{21,26,29–31,33,34,41,48,49} Global standardization and higher sensitivity could potentially be achieved with the recently developed next-generation flow (NGF) method⁵⁰ and with the establishment of accurate MRD response criteria.⁵¹ The NGF method is 1 to 2 log more sensitive than methods used in the studies included in the present analysis⁵⁰ and should therefore have greater prognostic value for improved survival and as a clinical end point, particularly among patients with high-risk features. The same argument applies regarding transitioning from allele-specific oligonucleotide–polymerase chain reaction to next-generation sequencing (NGS) for molecular-based MRD assessment.^{27,32} Large datasets with mature follow-up using both NGF and NGS to monitor MRD will be available in the future and should address whether one method is more informative than the other or whether they provide equivalent results.

It is important to note that flow- and molecular-based MRD monitoring evaluate single BM aspirates and do not assess extramedullary disease, which might explain why some patients achieve MRD negativity (by flow cytometry,^{21,26,34} allele-specific oligonucleotide–polymerase chain reaction,³⁷ or NGS^{21,27}) in the BM despite a persistent M-component. However, positron emission tomography/computed tomography–negative, immunofixation–positive patients have also been reported^{52,53} and, together with our findings that patients who were MRD negative, M-component positive had similar outcomes to patients who were MRD-negative in CR, this suggests that part of such discordances result from long M-protein half-lives.⁵⁴ In our analyses, approximately two thirds of all patients with MRD-negative disease who had nCR/PR subsequently achieved CR (data not shown). Studies are warranted to define how best to combine medullary and extramedullary MRD assessments.

Although the flow-MRD methods used in this study have lower sensitivity versus NGF and sequencing techniques, it was notable that achievement of 10-year PFS was almost exclusively seen in patients with MRD-negative disease (Fig 2C). With the long follow-up in GEM2000 patients, we were able to demonstrate that operational cure (ie, PFS > 10 years) seemed feasible in 11% of transplant-eligible patients with MM before the era of novel agents, particularly among patients presenting with a benign phenotypic BM signature at diagnosis plus MRD negativity after HDT/ASCT. Our data suggest a remarkable clinical

benefit from attaining deep remissions after intensive treatment in patients with favorable biology. These findings reinforce the notion that patients with more indolent biology benefit most from intensive treatment strategies followed by deep responses. Because traditional end points, such as PFS and OS, seem significantly prolonged in this patient population, sustained MRD negativity may emerge as a new end point in this setting.

Improved induction treatments are associated with higher MRD-negative rates, which should translate into better outcomes. If the prognostic impact of MRD negativity is independent of treatment, as shown here and elsewhere,³⁵ outcomes with different therapeutic strategies may be linked to probability of achieving MRD negativity, and thus treatment choice should be driven by the expected rates of MRD negativity.

In summary, on the basis of our findings from a large series of patients with MM with lengthy follow-up, we demonstrated that MRD negativity surpasses CR as a prognostic marker for PFS and OS across the spectrum of patients with MM and should be considered a key end point for both transplant-eligible and fit elderly patients with MM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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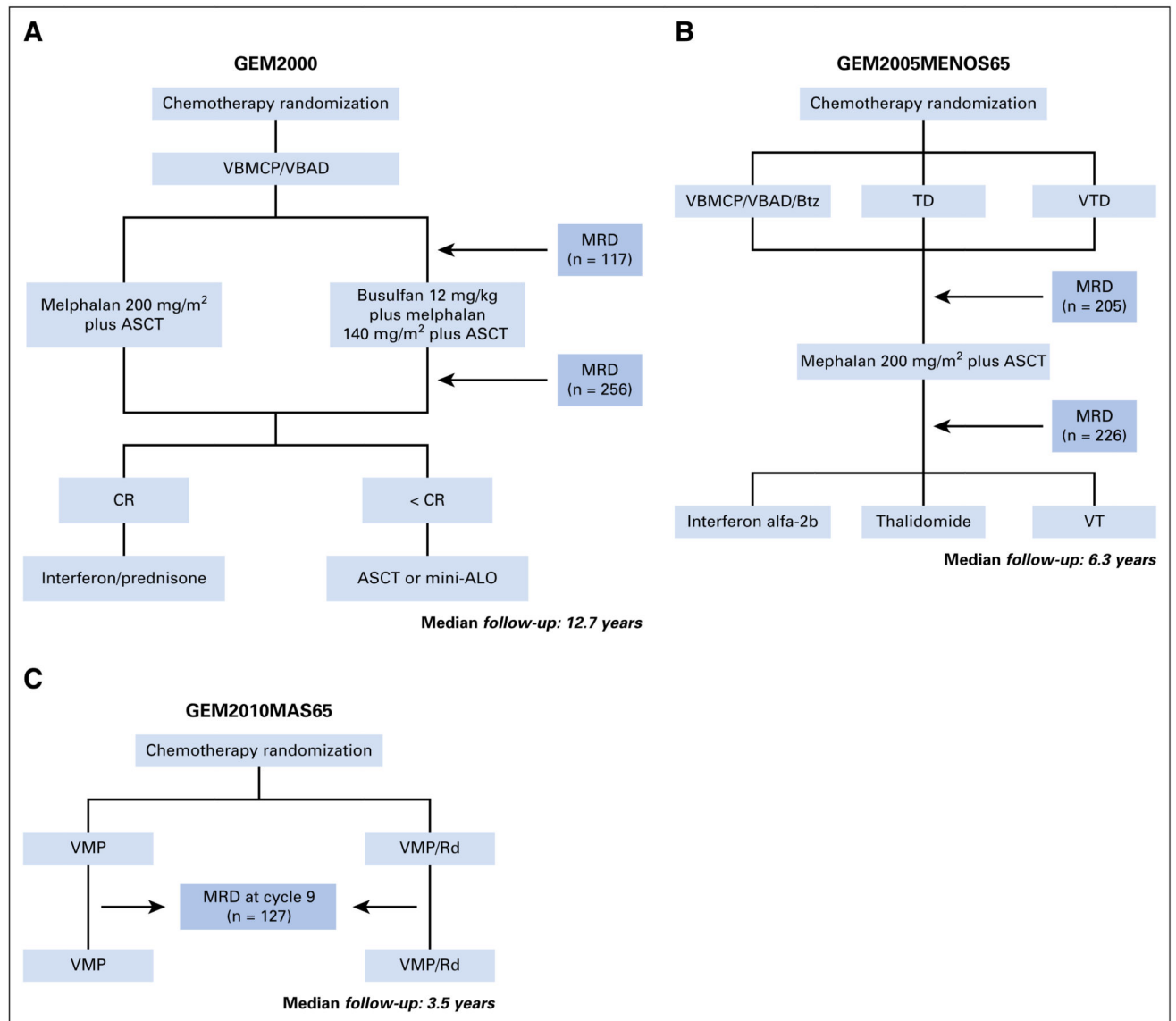
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**Fig 1.**

(A) PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) GEM (Grupo Español de Mieloma) 2000, (B) GEM2005MENOS65, and (C) GEM2010MAS65 study designs, showing the timing of minimal residual disease (MRD) assessments and numbers of patients included in the present analyses. Data and procedures of all these GEM clinical trials were subject to supervision by a qualified and independent external company. ALO, mini allogeneic stem cell transplant; ASCT, autologous stem cell transplantation; Btz, bortezomib; CR, complete remission; Rd, lenalidomide, dexamethasone; TD, thalidomide, dexamethasone; VBMCP/VBAD, vincristine, carmustine, cyclophosphamide, prednisone/vincristine, carmustine, doxorubicin, dexamethasone; VMP, bortezomib, melphalan, prednisone; VT, bortezomib, thalidomide; VTD, bortezomib, thalidomide, dexamethasone.

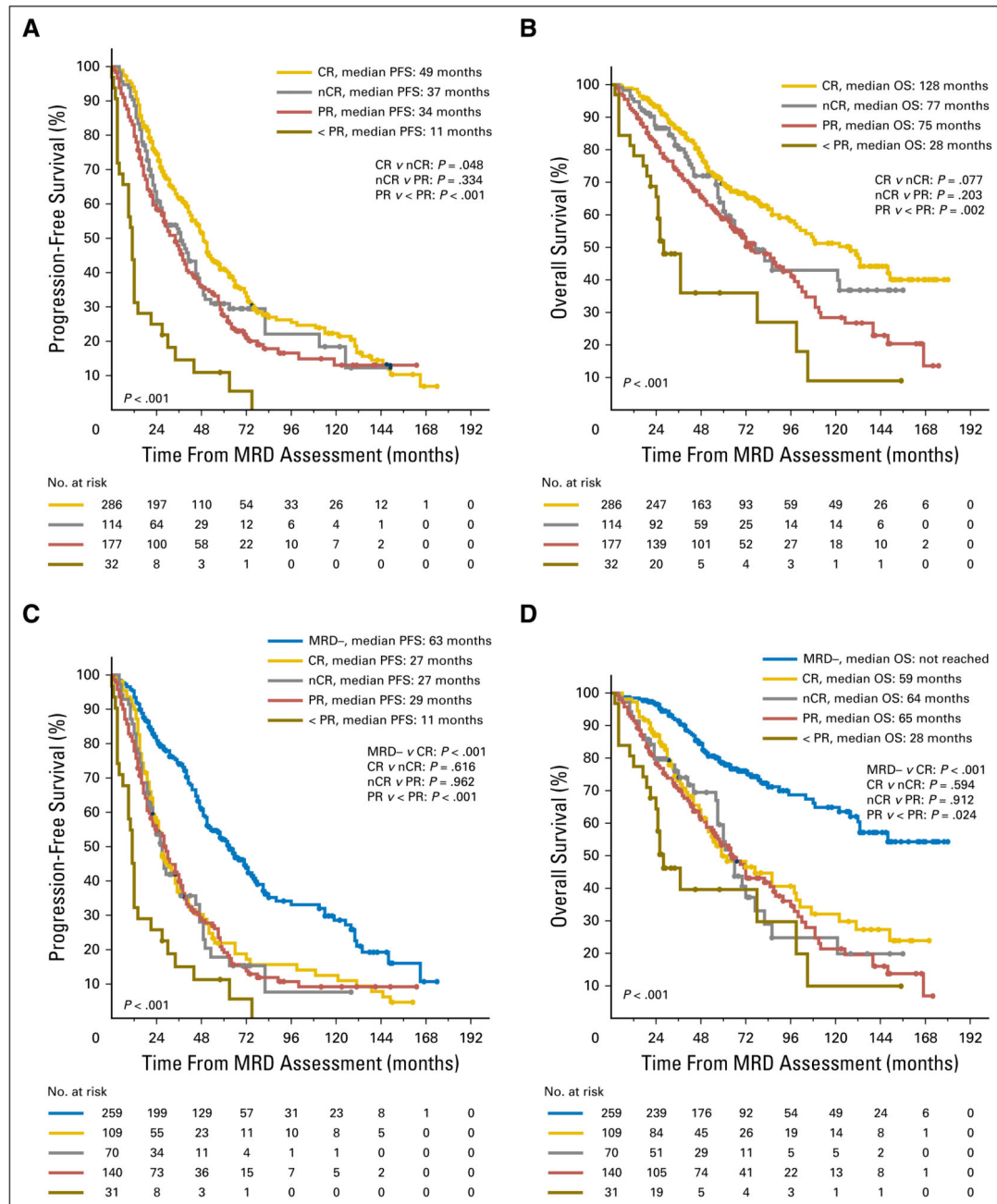


Fig 2. (A) Progression-free survival (PFS) and (B) overall survival (OS) from time of minimal residual disease (MRD) assessment (9 months after study enrollment) per conventional response assessment: less than partial response (< PR), partial response (PR), near-complete response (nCR) and complete response (CR). (C) PFS and (D) OS with MRD negativity (MRD-) status in addition to conventional response criteria.

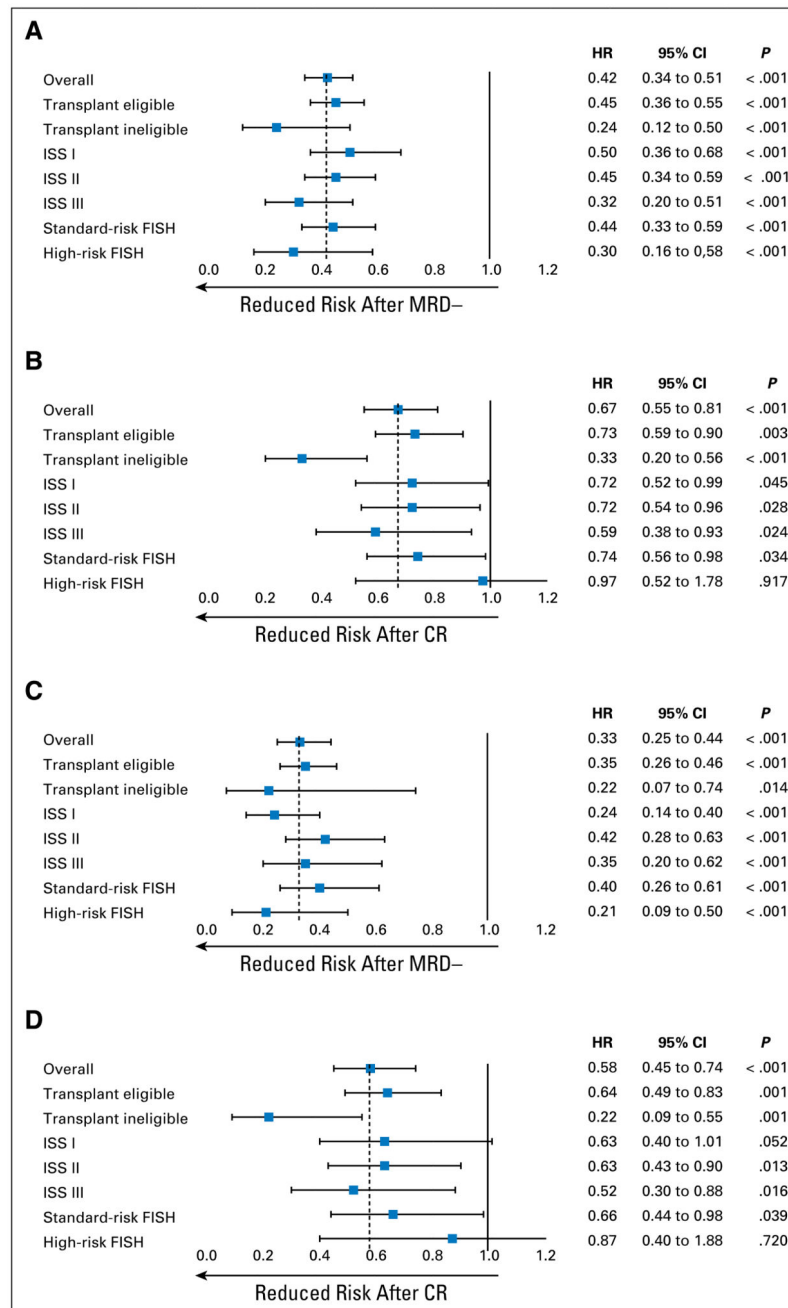


Fig 3. Forest plots of hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS) from time of minimal residual disease (MRD) assessment (9 months after study enrollment) according to achievement of MRD negativity (MRD-) or complete response (CR), among patient subgroups stratified by treatment (transplant *v* no transplant), International Staging System (ISS) disease stage, and standard-risk versus. high-risk (any t[4;14], t[14;16], and/or del[17p]) cytogenetics by fluorescent in situ hybridization (FISH).

(A) PFS by MRD-; (B) PFS by CR achievement; (C) OS by MRD-; (D) OS by CR achievement.

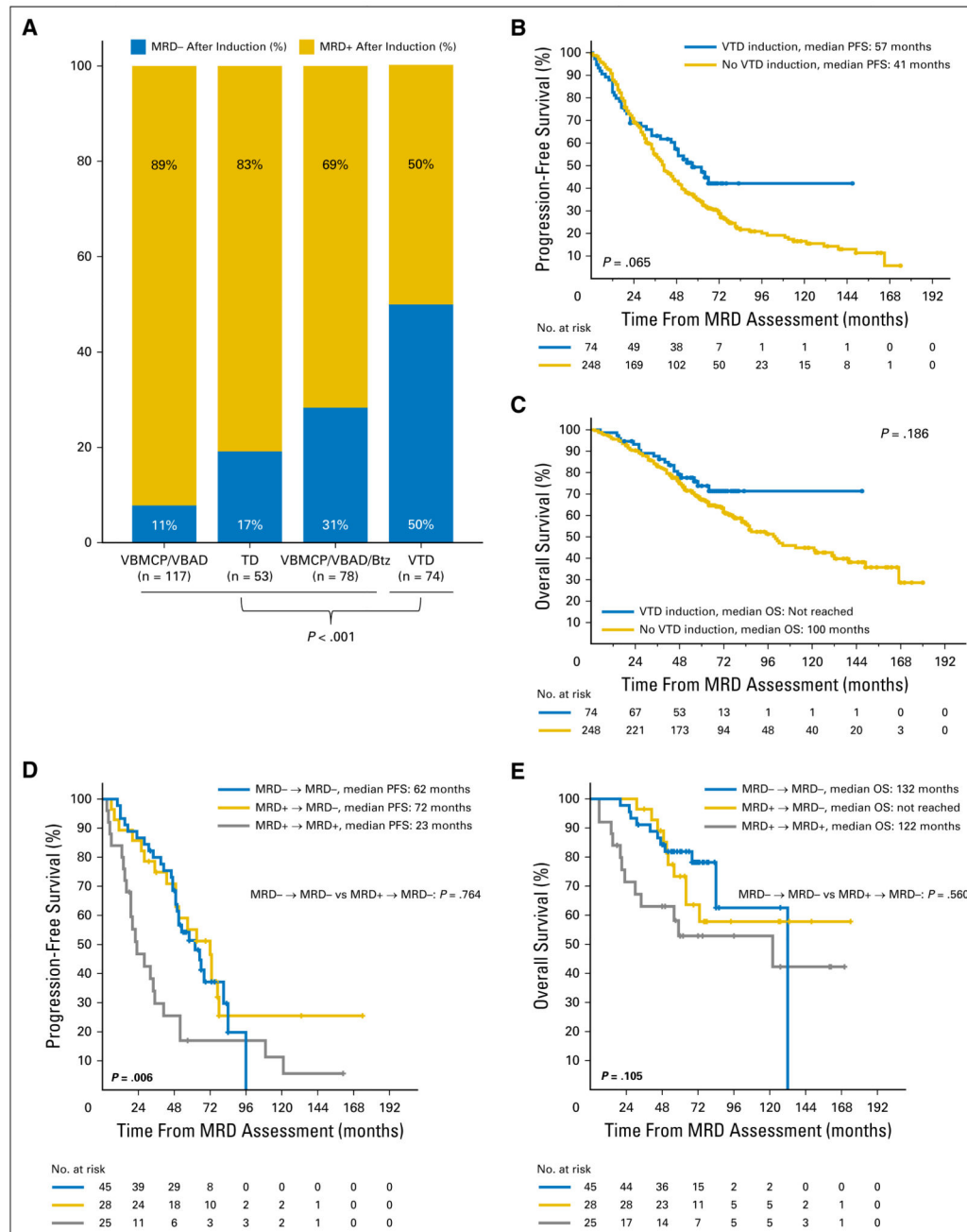


Fig 4. (A) Minimal residual disease (MRD)-negative (MRD-) and MRD-positive (MRD+) rates after induction with vincristine, carmustine, cyclophosphamide, prednisone/vincristine, carmustine, doxorubicin, and dexamethasone (VBMCP/VBAD), thalidomide and dexamethasone (TD), VBMCP/VBAD followed by two courses of bortezomib (VBMCP/VBAD/Btz), or bortezomib, thalidomide, dexamethasone (VTD) before high-dose therapy and autologous stem cell transplantation (n = 322). MRD- rates after VTD were significantly superior versus other induction regimens. Patients receiving VTD induction

displayed trends for superior (B) progression-free survival (PFS) and (C) overall survival (OS) from time of MRD assessment. (D) PFS and (E) OS among transplant-eligible patients in CR after induction, stratified into subgroups who were MRD⁻ before and after HDT/ASCT (MRD⁻ → MRD⁻), who attained MRD⁻ after HDT/ASCT (MRD⁺ → MRD⁻), and who were MRD⁺ before and after HDT/ASCT (MRD⁺ → MRD⁺).

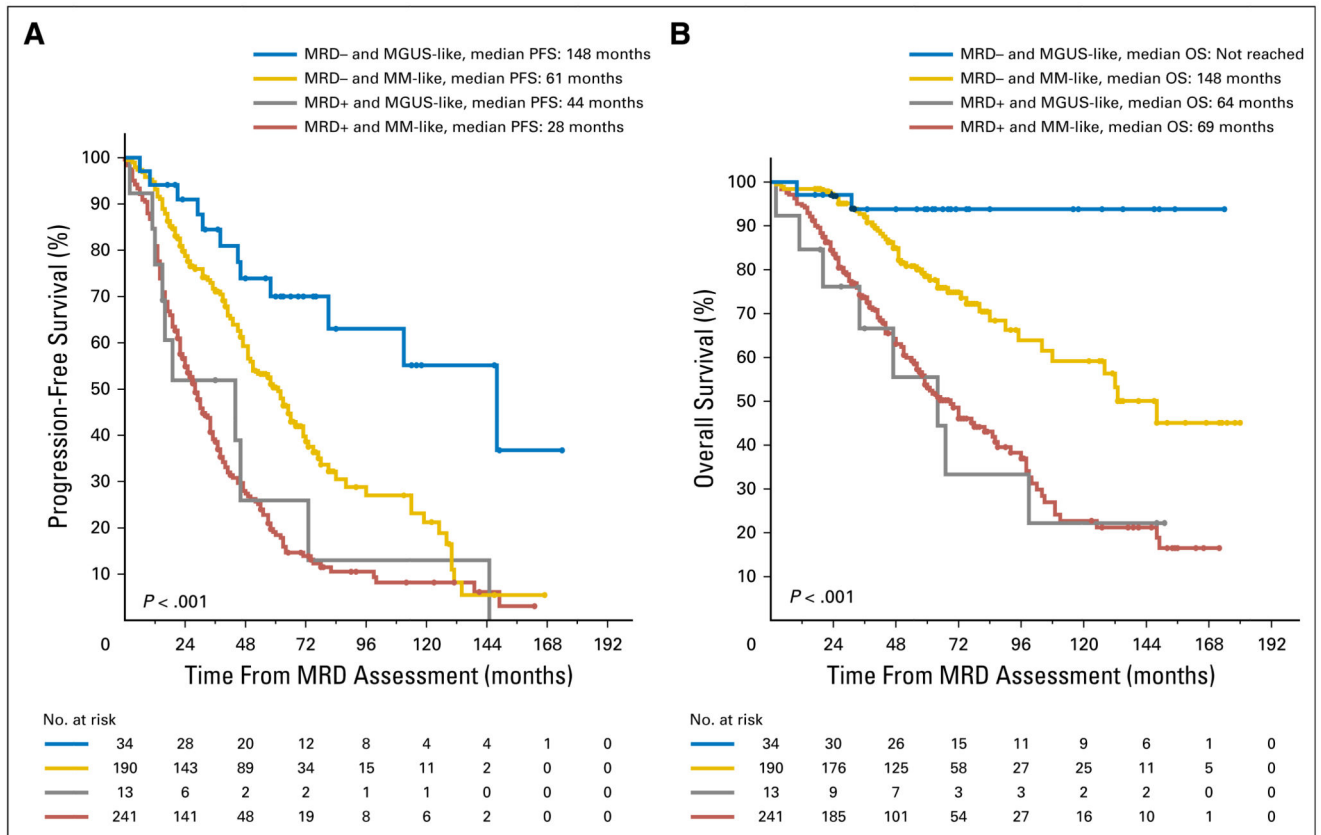


Fig 5. (A) Progression-free survival (PFS) and (B) overall survival (OS) from time of minimal residual disease (MRD) assessment (9 months after study enrollment) among patients with baseline monoclonal gammopathy of undetermined significance (MGUS)-like versus multiple myeloma-like bone marrow phenotypic profiles, according to MRD status. MM, multiple myeloma; MRD-, MRD-negative; MRD+, MRD-positive.

Table 1

Comparison of Cox Models for Progression-Free Survival and Overall Survival From Time of MRD Assessment (9 months after study enrollment) According to Depth of Response Defined by CR or MRD Status

Statistics	Progression-Free Survival			Overall Survival		
	CR	MRD	Difference (MRD – CR)	CR	MRD	Difference (MRD – CR)
HR (95% CI)	0.75 (0.58 to 0.97)	0.40 (0.31 to 0.53)	—	0.70 (0.49 to 0.99)	0.30 (0.20 to 0.44)	—
LL (null)	–1,284.4345	–1,284.4345	—	–695.16501	–695.16501	—
LL (model)	–1,270.6986	–1,250.0463	20.6523	–662.03031	–643.54398	–18.48633
LR χ^2	27.47	68.78	41.31	66.27	103.24	36.97
Harrell C	0.6156	0.6668	0.0512	0.7115	0.7551	0.0436
Somer D	0.2311	0.3336	0.1025	0.4231	0.5103	0.0872
AIC	2,554.775	2,514.093	–40.682	1,338.061	1,301.088	–36.973
BIC	2,582.074	2,541.392	–40.682	1,365.36	1,328.387	–36.973

NOTE. Both models were adjusted for age, transplant-eligibility, International Staging System disease stage, lactate dehydrogenase level, and fluorescence in situ hybridization cytogenetics. Calibration of each model was assessed graphically by comparing observed (Kaplan-Meier method) and predicted survival probabilities. The difference in Harrell C was statistically significant for both progression-free survival and overall survival (bootstrap test, 10,000 replicates: $P < .002$ and $P = .004$, respectively).

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CR, complete remission; HR, hazard ratio; LL, log likelihood; LR, logistic regression; MRD, minimal residual disease.