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ARTICLE

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High-risk features of early relapse in newly-diagnosed multiple myeloma: The impact of cytogenetics and response to initial therapy

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Abstract

Patients with newly-diagnosed multiple myeloma (MM) who experience early relapse (ER) have dismal overall survival (OS). Their prospective identification, either before or soon after treatment initiation, is paramount to use alternative approaches and prevent ER. In this study, we investigated the frequency and disease characteristics of ER during the first 18 months after treatment initiation (ER18), in a series of 1215 newly-diagnosed MM patients enrolled in four PETHEMA/GEM clinical trials for the transplant-eligible and transplant-ineligible populations. ER18 was observed in 266 of the 1215 patients (22%) and resulted in a median OS of 19 versus 114 months in cases without ER18. When compared to the ISS and the presence of ≥2 high-risk cytogenetic abnormalities, a modified version of the new high-risk definition from the International Myeloma Society (mHR-IMS) showed the most balanced negative and positive predictive values of ER18 (83.5% and 40%, respectively). In addition to the mHR-IMS, an ECOG = 2, ISS 3, and calcium levels ≥ 11 mg/dL were independently associated with ER18. These variables were modeled into a predictive score in which the rates of ER18 were 2%, 24.5%, and 59% in patients with low-, intermediate-, and high-risk score. The risk of ER18 and OS were modulated by the VGPR status at 6–9 months after treatment initiation. In conclusion, we present a risk model that predicts ER18 and can be readily applied in clinical trials and routine practice to identify treatment strategies empowered to prevent ER18 and improve survival outcomes of newly-diagnosed patients with functional high-risk MM.

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INTRODUCTION

Current options for the treatment of multiple myeloma (MM) achieve very high response rates and an increasing number of patients experiences long-term survival.[1–5] Thus, more than ever there is a pressing need to better characterize patients who show early relapse (ER), which usually predicts a more aggressive disease and dismal survival.[6–9] Bridging the gap between these patients and those who experience longer progression-free survival (PFS) and overall survival (OS) is one of the greatest challenges in MM.

There is no consensus on the appropriate definition of ER. It has been typically proposed as a relapse occurring within 12–24 months from treatment initiation in newly-diagnosed patients.[6–8,10–17] Thus, one possible definition of ER would be disease progression within 18 months after treatment initiation (ER18), which would be applicable to transplant-ineligible and transplant-eligible patients, since this time point would overlap with a period of 12 months post-autologous transplant. Of note, most studies characterized ER in transplant-eligible patients but the role of high-dose melphalan is being questioned in some countries due to the efficacy of novel regimens. Accordingly, new approaches to predict ER regardless of transplant eligibility are needed.

The most common risk factors of ER include advanced staging, high tumor burden, and the presence of high-risk cytogenetics. However, these are risk factors defined at diagnosis and do not capture the modulation of patients' risk during treatment. Response to initial therapy is a relevant prognostic factor in MM, but its role in redefining patients at risk of ER remains uncertain. In this study, we aimed at predicting ER18 in newly-diagnosed transplant-eligible and transplant-ineligible patients by developing a risk model based on parameters readily available at diagnosis. Additionally, we assessed the impact of response to frontline therapy in patients at risk of ER18.

PATIENTS AND METHODS

Study design

Patients were enrolled in four consecutive PETHEMA/GEM clinical trials for those who were transplant-eligible (GEM2005MENOS65 and GEM2012MENOS65) and transplant-ineligible (GEM2005MAS65 and GEM2010MAS65). The inclusion criteria, design, procedures, treatment, and outcomes of each trial have been previously described and are summarized in Supplemental Table 1.[18–22] Patients with a follow-up shorter than 18 months ($n = 26$) or patients who died for reasons other than disease progression ($n = 14$) during this period were excluded from the analysis. Thus, all patients who died without disease progression and were included in the study had a follow-up time longer than 18 months. Clinical trials were registered in ClinicalTrials.gov (NCT00443235, NCT00443235, NCT00461747, and NCT01916252), and data were centrally assessed and monitored by an external contract research organization. The median follow-up of the study population was 58 months (interquartile range 37.4–70.5).

Assessments

At diagnosis, the following patient' and disease characteristics were computed: gender, age (<65 vs. ≥65 years), the Eastern Cooperative Oncology Group (ECOG) performance status, hemoglobin (<10 vs. ≥10 mg/dL), creatinine (<1.1 vs. ≥1.1 mg/dL), calcium (<11 vs. ≥11 mg/dL), albumin (<3.5 vs. ≥3.5 g/dL), Beta-2 microglobulin (<3.5 vs. ≥3.5 mg/L and <5.5 vs. ≥5.5 mg/L), lactate dehydrogenase (LDH) levels normal or higher than the upper limit of the normal (UNL) range, the heavy and light chain isotype of the M component, presence of urine light chains, the percentage of bone marrow plasma cells (BMPCs) by morphology (<60% vs. ≥60%), circulating plasma cells (none or low [<0.2%] vs. high levels [≥0.2%]), the presence versus absence of plasmacytomas, the International staging system (ISS), revised-ISS (R-ISS), and the presence versus absence of the high-risk cytogenetic alterations (HRCA) del(17p), t(4;14), and/or t(14;16). The impact of gain(1q) and del(1p) was also analyzed. The cumulative effect of having <2 versus ≥2 HRCA (including alterations in chromosome 1) was also considered. FISH was performed in CD138-selected BMPCs. The cutoff values were 10% for IgH translocations (fusion/break-apart probes), gain(1q), and del(1p) and 20% for del(17p). Additionally, for patients with gain(1q), 1q amplification [amp(1q)] was defined as four or more copies of 1q.

The upcoming high-risk definition proposed by the International Myeloma Society (IMS)[23] classifies patients into standard versus high-risk based on the presence of either (i) del(17p) in >20% BMPC and/or *TP53* mutations; (ii) an IgH translocation [t(4;14) or t(14;16) or t(14;20)] along with +1q and/or del(1p); (iii) monoallelic del(1p32) along with +1q, or bi-allelic del(1p32); and (iv) the presence of β2 microglobulin ≥5.5 mg/L with normal creatinine (<1.2 mg/dL). We aimed at assessing the impact of the new IMS classification to predict ER18 and, accordingly, modeled a new variable coined as modified high-risk IMS (mHR-IMS) due to the absence of information on *TP53* mutations and bi-allelic del(1p32) in our series.

Quantification of circulating tumor cells (CTCs) was performed using EuroFlow next-generation flow cytometry[24] and the optimal threshold for the prediction of ER18 was determined using a ROC curve.

Responses were evaluated according to the European Group for Blood and Marrow Transplantation and IMWG criteria.[25–27] The assessment of minimal residual disease (MRD) was evaluated by flow cytometry with a sensitivity level ranging between 10^{-4} and 10^{-5} in the GEM2005MENOS65, GEM2005MAS65, and GEM2010MAS65 clinical trials and 2×10^{-6} in the GEM2012MENOS65 trial.

Statistical analysis

The prognostic impact of ER18 in PFS and OS was analyzed using Cox regressions and the Kaplan–Meier method was used to describe the distribution of survival time based on risk score categories. PFS was analyzed as time of study entrance until disease progression or death from any cause. OS was measured as the time of study entrance until

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death from any cause. Additional analysis exploring the impact of achieving a very good partial response or better (≥VGPR) was landmarked at 6 months.

We used means with standard deviations and proportions to summarize demographic and clinical characteristics of the patients. A univariate logistic regression was performed to investigate the association between patient' and disease characteristics with ER18. Statistically significant variables were selected for multivariate models. The *p* values less than 0.05 were considered statistically significant.

The multivariable logistic regression with backward stepwise selection was used for predictor selection during modeling. A *p* value of 0.1 was establish as the significance level for removal from the model. The area under the receiver-operating characteristic curve (AUC) quantified the performance of the multivariable model. Internal validation of new risk models was performed using bootstrapping with 500 repetitions.

Statistical analyses were performed using Stata (StataCorp, 2023; Stata Statistical Software: Release 18; College Station, TX: StataCorp LLC).

RESULTS

Of the 1215 newly-diagnosed MM patients analyzed in this study, 266 (22%) showed ER within 18 months from treatment initiation and hereafter comprise the ER18 group. The remaining patients (*n* = 949, 78%) either progressed beyond 18 months, died without disease progression beyond 18 months, or had ongoing response at the time of this analysis and were included as the reference group for comparison with the ER18 group.

The median PFS and OS in the overall cohort (*n* = 1215) was 43.7 months (95% confidence interval [CI] 40–47.4) and 94.6 months (95% CI 82–105), respectively. The median PFS in the ER18 group was 7.85 months (95% CI 7.3–8.8) versus 59.20 months (95% CI 55–63.9) in the reference group. The median OS in the ER18 group was 19.2 months (95% CI 17–21) versus 114.4 months (95% CI 105 to NR) in the reference group.

Baseline characteristics of the two groups are described in Table 1. As compared to the reference population, patients with ER18 showed more frequently β2-microglobuline levels ≥ 5.5 mg/L, hemoglobin < 10 g/dL, and high LDH.

ER18 was also associated with a higher percentage of BMPC and CTCs, as well as higher frequency of ISS 3, R-ISS 3, and HRCA according to IMWG criteria. The presence of ≥2 HRCA and mHR-IMS was more frequently observed in patients with ER18 versus the reference population. The rates of ≥VGPR and MRD negativity were lower in the ER18 versus the reference group (Table 1).

Results of the univariate analysis performed in the 793 patients with complete cytogenetic data are described in Table 2. The following baseline variables were associated with higher probability of ER18: R-ISS 3 (OR 4.6 [95% CI 2.7–7.8], presence of ≥2 HRCA (OR 3.6, 95% CI 2.4–5.4), mHR-IMS (OR 3.4, 95% CI 2.3–4.9), ISS 3 (OR 2.9 [95% CI 2.0–2.4], ECOG = 2 (OR 2.43, 95% CI 1.7–3.6), HRCA (OR 2.3, 95% CI 1.7–3.2), elevated LDH (OR 2.2 [95% CI 1.6–3.1]), calcium ≥ 11 mg/dL (OR 2.2 [95% CI 1.4–3.3]), hemoglobin < 10 g/dL (OR 1.93, 95% CI 1.5–2.6), creatinine ≥ 1.5 mg/dL (OR 1.56, 95% CI 1.0–2.5), BMPC ≥ 60% (OR 1.44, 95% CI 1.0–2.0), and >0.2% CTCs (OR 2.07, 95% CI 1.1–4.0). Achieving ≤ VPGR (OR 5.02, 95% CI 3.6–6.7) and persistence of MRD (OR 3.96, 95% CI 2.2–7.0) were also associated with higher probability of ER18.

The predictive values of the composite ISS and IMWG cytogenetic classifications were subsequently analyzed. The frequency of ER18 was higher in patients with ISS 3 (32%; *n* = 92/288), as

TABLE 1 Patient characteristics of the overall population, stratified according to the ER18 outcome. (continued on next page)

Characteristic	Overall population	ER18 population (*N* = 266)	Reference population (*N* = 949)	*p* value
Age years (mean, SD)	62.9 (10.5)	64.5 (10.3)	62.5 (10.5)	
Age < 65, *n* (%)	709 (58.4)	144 (54.1)	565 (59.5)	0.114
Age ≥ 65, *n* (%)	506 (41.7)	122 (45.9)	384 (40.5)	
ASCT, *n* (%)				
TE	747 (61.5)	155 (58.3)	592 (62.4)	0.223
NTE	468 (38.5)	111 (41.7)	357 (37.6)	
Sex, *n* (%)				
Male	637 (52.4)	129 (48.5)	508 (53.5)	0.146
Female	578 (47.6)	137 (51.5)	441 (46.5)	
ECOG, *n* (%)				
0	429 (35.4)	69 (26.0)	360 (38.0)	<0.001
1	572 (47.2)	129 (48.7)	443 (46.8)	
2	211 (17.41	67 (25.3)	144 (15.2)	
ISS, *n* (%)				
I	409 (34.0)	57 (21.7)	352 (37.5)	<0.001
II	505 (42.0)	114 (43.4)	391 (41.6)	
III	288 (24.0)	92 (35.0)	196 (20.9)	
R-ISS, *n* (%)				
I	276 (26.0)	32 (13.4)	244 (29.7)	<0.001
II	679 (64.0)	167 (69.9)	512 (62.2)	
III	107 (10.1)	40 (16.7)	67 (8.1)	
Myeloma subtype				
IgG	710 (58.6)	154 (57.9)	556 (58.8)	0.717
IgA	320 (26.4)	75 (28.2)	245 (25.9)	
IgM	1 (0.08)	0 (0.0)	1 (0.1)	
IgD	163 (1.5)	33 (12.4)	130 (13.8)	
Bence-Jones	11 (0.9)	4 (1.5)	7 (0.7)	
Non-secretory	6 (0.5)	0 (0.0)	6 (0.6)	
Light chain subtype, *n* (%)				
Kappa	754 (62.6)	161 (60.5)	593 (63.2)	0.435
Lambda	451 (37.4)	105 (39.5)	346 (36.9)	
Albumin (g/dL), mean (SD)	3.6 (1.5)	3.4 (0.7)	3.7 (1.6)	
Albumin < 3.5 g/dL, *n* (%)	482 (40.0)	136 (51.3)	346 (36.7)	<0.001
Albumin ≥ 3.5 g/dL, *n* (%)	726 (60.1)	129 (48.7)	597 (63.3)	
B2m (mg/L), mean (SD)	4.5 (3.6)	5.5 (4.0)	4.3 (3.4)	
B2m ≥ 5.5 mg/L, *n* (%)	288 (24.0)	92 (35.0)	196 (20.9)	<0.001
LDH (UI/L)				
<UNL, *n* (%)	1030 (85.2)	202 (76.2)	828 (87.7)	<0.001
≥UNL, *n* (%)	179 (14.8)	63 (23.8)	116 (12.3)	
Hemoglobin (g/dL), mean (SD)	10.9 (1.9)	10.5 (1.8)	11.1 (1.9)	<0.001
Hemoglobin < 10 g/dL, *n* (%)	45 (37.4)	132 (49.8)	320 (33.9)	<0.001
Calcium (mg/dL), mean (SD)	9.4 (2.1)	9.4 (2.0)	9.4 (2.2)	0.852
Calcium ≥ 11 mg/dL, *n* (%)	104 (8.5)	37 (14.0)	66 (7.0)	<0.001

TABLE 1 (Continued)

Characteristic	Overall population	ER18 population (*N* = 266)	Reference population (*N* = 949)	*p* value
Creatinine (mg/dL), mean (SD)	1 (0.3)	1.0 (0.4)	1.0 (0.3)	0.125
Creatinine ≥ 1.5 mg/dL, n (%)	126 (10.4)	37 (14.0)	89 (9.4)	0.033
Lytic lessions, *n* (%)				
Yes	878 (75.6)	193 (77.8)	685 (74.9)	0.350
No	284 (24.4)	55 (22.2)	229 (25.1)	
Plasmacytomas, *n* (%)				
Yes	126 (19.2)	23 (23.0)	103 (18.56	0.300
No	529 (80.8)	77 (77.0)	452 (81.4)	
BMPCs-MORF, mean (SD)	37.6 (26.2)	40.3 (26.7)	36.9 (26.0)	
<60, n (%)	892 (77.6)	175 (72.3)	717 (70.0)	0.028
≥60, n (%)	258 (22.4)	67 (27.7)	191 (21.0)	
CTC, *n* (%)				
Negative or positive low	297 (82.5)	39 (72.2)	258 (84.3)	0.034
Positive high	63 (17.5)	15 (27.8)	48 (15.7)	
del(17p), t(4;14) and/or t(14;16), *n* (%)				
Yes	224 (21)	79 (32.9)	145 (17.5)	<0.001
No	845 (79.0)	161 (67.1)	684 (82.5)	
<2 versus ≥ 2 HRCA (including alterations in chromosome 1), *n* (%)				
Yes	127 (14.8)	54 (30.3)	73 (10.8)	<0.001
mHR-IMS, *n* (%)				
Yes	158 (18.4)	63 (35.4)	96 (14.1)	<0.001
No	699 (81.6)	115 (64.6)	583 (85.9)	
Double hit mHR-IMS, *n* (%)				
del(17p) + other categories	40 (4.7)	21 (11.8)	19 (2.8)	<0.001
Response after induction, *n* (%)				
sCR/CR/VGPR	624 (53.0)	56 (23.4)	568 (60.6)	<0.001
MRD Ind negative, *n* (%)	292 (32.0)	14 (12.0)	278 (35.0)	<0.001

Note: Plasmacytomas refers to both para-medullary and extramedullary disease.

Abbreviations: ASCT, autologous stem-cell transplantation; BMPCs, bone marrow plasma cells; BMPCs-MORF, BMPCs by morphology; b2m, beta 2-microglobulin; CR, complete response; del(17p), 17p deletion; del(1p), 1p deletion; ECOG, Eastern Cooperative Oncology Group Performance status scale; ER18, early relapse within 18 months from diagnosis; HRCA, high-risk cytogenetics abnormality; HRCA IMWG, high-risk cytogenetics abnormality defined by IMWG; IMS, International Myeloma Society; IMWG, International Myeloma Working Group; ISS, International Staging System; LDH, lactate dehydrogenase; mHR-IMS, modified high-risk IMS; MRD-Ind, minimal residual disease after induction; NTE, non-transplant eligible; PD, progressive disease; PR, partial response; R-ISS, Revised International Staging System; sCR, stringent complete response; SD, stable disease; t, translocation; TE, transplant-eligible; UNL, upper limit of normal; VGPR, very good partial response.

compared to those with stages II and I (22%; *n* = 114/505 and 14%; *n* = 57/409, respectively) ($p < 0.001$). The frequency of patients with ER18 having del(17p), t(4;14), and/or t(14;16) was 35% (*n* = 79/224) versus 7% (*n* = 161/845) in those without any of these HRCA ($p < 0.001$). The frequency of patients with ER18 having <2 HRCA was 17% (*n* = 124/730) versus 42% (*n* = 54/127) if ≥2 HRCA ($p < 0.001$). The frequency of patients with ER18 having modified

TABLE 2 Univariate analysis of the baseline features to predict ER18.

Characteristic	Category	OR	CI (95%)	*p* value
Age ≥ 65		1.25	0.95–1.64	0.115
Age ≥ 80		1.23	0.65–2.35	0.526
ASCT	Yes	0.84	0.64–1.11	0.224
Sex	Male	1.22	0.93–1.61	0.147
ECOG	1	1.52	1.10–2.10	0.011
	2	2.43	1.65–3.58	0.000
ISS	I	Ref.		
	II	1.80	1.27–2.55	0.001
	III	2.90	1.99–4.21	0.000
R-ISS	I	Ref		
	II	2.49	1.65–3.74	0.000
	III	4.55	2.66–7.79	0.000
Light chain subtype	L	1.12	0.85–1.48	0.435
Albumin < 3.5 g/dL		1.82	1.38–2.39	0.000
B2m ≥ 3.5 mg/L		2.01	1.51–2.68	0.000
B2m ≥ 5.5 mg/L		2.04	1.51–2.75	0.000
LDH ≥ UNL		2.23	1.58–3.14	0.000
Hemoglobin < 10 g/dL		1.93	1.47–2.55	0.000
Calcium ≥ 11 mg/dL		2.16	1.41–3.31	0.000
Creatinine ≥ 1.5 mg/dL		1.56	1.03–.35	0.034
Lytic lessions	Yes	1.17	0.84–1.64	0.350
Plasmacytomas	Yes	1.31	0.79–2.19	0.301
BMPCs-MORF ≥ 60		1.44	1.04–1.99	0.028
CTC positive	High	2.07	1.06–4.04	0.034
del(17p)	Yes	3.03	1.93–4.76	0.000
t(4;14)	Yes	1.90	1.29–2.81	0.001
t(14,16)	Yes	2.37	1.13–4.99	0.023
Gain(1q)	Yes	1.53	1.10–2.13	0.012
del(1p)	Yes	2.38	1.28–4.43	0.006
del(17p), t(4;14) and/or t(14;16)	Yes	2.31	1.68–3.20	0.000
≥2 HRCA (including alterations in chromosome 1)	Yes	3.62	2.42–5.40	0.000
mHR-IMS	Yes	3.37	2.31–4.90	0.000
del(17p) + other categories mHR-IMS	p53+others	5.60	2.92–10.75	0.000
Response after induction	PR/SD/PD versus VGPR/ CR/sCR	5.02	3.62–6.95	0.000
MRD Induction	Positive	3.96	2.22–7.04	0.000

Abbreviations: ASCT, autologous stem-cell transplantation; BMPCs, bone marrow plasma cells; BMPCs-MORF, BMPCs by morphology; b2m, beta 2-microglobulin; CI, confidence interval; CR, complete response; CTC, circulating tumor cells; del(17p); 17p deletion; del (1p), 1p deletion; ECOG, Eastern Cooperative Oncology Group Performance Status Scale; ER18, early relapse within 18 months from diagnosis; HRCA, High-risk cytogenetics abnormality; HRCA IMWG, High-risk cytogenetics abnormality defined by IMWG; IMS, International Myeloma Society; IMWG, International Myeloma Working Group; ISS, International Staging System stage; L, Lambda; LDH, lactate dehydrogenase; mHR-IMS, modified high-risk IMS; MRD-Ind, minimal residual disease after induction; PD, progressive disease; PR, partial response; R-ISS, Revised International Staging System stage; sCR, stringent complete response; SD, stable disease; t, translocation; UNL, upper limit of normal; VGPR, very good partial response.

standard-risk IMS (mSR-IMS) was 16.4% ($n = 115/699$) versus 39.8% ($n = 63/158$) in those having mHR-IMS ($p < 0.001$). The negative predictive values (NPV) of ER18 in patients having ISS 1/2, <2 HRCA, and mSR-IMS were 81.3% (95% CI 78.6%–83.8%), 83% (95% CI 80.1–85.7%), and 83.5% (95% CI 80.6–86.2%), respectively. The positive predictive values (PPV) of ER18 in patients having ISS 3, ≥2 HRCA, and mHR-IMS were 31.9%, 42.5%, and 39.9%, respectively.

None of the existing risk classifications showed a nearly perfect capacity of predicting ER18. Thus, we performed multivariate analysis using the stepwise model to identify independent and complementary risk factors associated with ER18 for the development of a more predictive risk model. The covariates included were the diagnostic features significantly associated with a higher probability of ER18 in the univariate analysis. The presence of ECOG = 2 (OR 2.43, 95% CI 1.4–4.2), ISS 3 (OR 1.94; 95% CI 1.2–3.23), elevated calcium levels ≥ 11 mg/dL (OR 1.98, 95% CI 1.1–3.4), and the presence of mHR-IMS (OR 3.05, 95% CI 2.0–4.6) showed independent association with ER18 (Table 3). The AUC of the model including the statistically significant covariates was 0.706. Internal validation resulted in a nearly identical AUC (0.707). The predictive value of this model was statistically superior to that of the R-ISS (AUC 0.61, $p < 0.001$) and R2-ISS (AUC 0.66, $p = 0.005$).

The aforementioned variables were modeled into a prognostic score with three categories: low (0–2 points), intermediate (3–6 points), and high-risk (≥7 points), which classified 51%, 43%, and 6% of patients, respectively (Table 4). The respective frequency of ER18 in each category was 12% (reference), 24.5% (OR of 2.38, 95% CI 1.6–3.5), and 58.7% (OR 10.4, 95% CI 5.4–20.1). The median PFS and OS of patients with low-risk of ER18 was 60 months (95% CI 55–70) and not reached (95% CI 113 to NR). Cases with intermediate risk of ER18 showed a median PFS and OS of 40.7 (95% CI 33.5–46) and 79.6 (95% CI 70.8–102) months. The median PFS and OS of patients with high risk of ER18 was 8.7 (95% CI 6.4–21) and 29.3 (95% CI 17–54) months. The HR for PFS and OS for the different risk categories are shown in Figure 1A,B.

We next investigate if the risk of ER18 was modulated by the achievement of ≥VGPR landmarked at 6–9 months after treatment initiation. Achieving ≥VGPR or better was independently associated with a lower risk of ER18 (OR 0.18, 95% CI 0.1–0.3, $p < 0.001$) in the multivariate analysis described earlier. Thus, we next analyzed the impact of achieving ≥VGPR in each of the three risk categories defined earlier.

The rate of ≥VGPR progressively decreased in patients with low, intermediate, and high risk of ER18 (56%, 41%, and 31%, respectively). Considering the low-risk group achieving ≥VGPR as the reference, the OR of ER18 in low-risk patients who did not achieve ≥VGPR was 4.58 (CI 2.1–10). The OR of ER18 in intermediate-risk patients achieving ≥VGPR versus those who did not was 1.97 (CI 0.8–4.7) and 11.4 (CI 5.3–24.3), respectively. The OR of ER18 in high-risk patients achieving ≥VGPR versus those who did not was 7.85 (CI 2.3–26.3) and 29.4 (95% CI 6.7–128.6).

Patients with low risk of ER achieving ≥VGPR showed the best outcome with a median PFS of 97.5 months (95% CI 68 to NR) and OS not reached (95% CI 86 to NR). In contrast, patients with low risk of ER18 in less than VGPR showed a PFS superimposable to that of intermediate-risk patients achieving ≥VGPR, with medians of 43 (95% CI 33–54) and 52 months (95% CI 42–61), respectively (Figure 2A). Similar results were observed for OS (Figure 2B). The same occurred in intermediate-risk patients who did not achieve VGPR and high-risk patients achieving ≥VGPR, with overlapping median PFS of 20.7 (95% CI 17–28) and 19.8 months (95% CI 12–37), and median OS of 68 and 54 months. Patients with high risk of ER18 who did not achieve VGPR showed a median PFS of 2.7 months (95% CI 0.4–33) and dismal OS.

Achievement of MRD negativity at 6–9 months after treatment initiation was independently associated with lower risk of ER18 (OR 0.17, 95% CI 0.1–0.4, $p < 0.001$). Survival of patients with low, intermediate, and high risk of ER18 was modulated by MRD status. Accordingly, patients who achieved MRD negativity showed improved survival outcomes compared to those who remained MRD positive in each of the three groups (Figure S1). Among the 17 patients in VGPR with high risk of ER18 and MRD assessment, seven had undetectable MRD and five of them are still alive after a median follow-up of 63.6 months. In contrast, 7 out of the 10 patients with persistent MRD have died within 13–61 months.

TABLE 3 Multivariable analysis of the baseline features to predict ER18.

Variable (N = 793)	OR	CI (95%)	p value
ECOG 1	1.69	1.08–2.64	0.022
ECOG 2	2.43	1.41–4.19	0.001
ISS II	1.43	0.90–2.28	0.129
ISS III	1.94	1.16–3.23	0.011
LDH ≥ UNL	1.49	0.93–2.40	0.100
Calcium ≥ 11 mg/dL	1.98	1.14–3.44	0.016
BMPC ≥ 60%	1.47	0.97–2.22	0.073
mHR-IMS yes	3.05	2.01–4.64	0.000

Note: AUC: 0.7061.

Abbreviations: BMPC, bone marrow plasma cells; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status scale; ISS, International Staging System; LDH, lactate dehydrogenase; mHR-IMS, modified high-risk IMS; OR, odds ratio; PR, partial response; UNL, upper limit of normal.

TABLE 4 Weighted model to predict risk of ER18.

Variable	Points
ECOG 1	1
ECOG 2	2
ISS II	1
ISS III	2
LDH ≥ UNL	1
Calcium ≥11 mg/dL	2
BMPC ≥ 60%	1
mHR-IMS yes	3

Note: Low risk: 0–2 points; intermediate risk: 3–6 points; high risk: ≥7. The internal validation resulted in a correction of the AUC from 0.706 to 0.707.

Abbreviations: BMPC, bone marrow plasma cells; ECOG, Eastern Cooperative Oncology Group performance status scale; ISS, International Staging System; LDH, lactate dehydrogenase; mHR-IMS, modified high-risk IMS; UNL, upper limit of normal.

DISCUSSION

ER is one of the most important risk factors associated with inferior OS in patients with newly-diagnosed MM. These patients are considered to have functional high risk, and their prospective identification may facilitate the adoption of individualized therapeutic strategies to improve the dismal survival.

The timing for the optimal definition of ER is not clearly established, with definitions ranging from relapse within 12–24 months after treatment initiation or after autologous transplant. However, the traditional patient stratification into transplant-eligible and

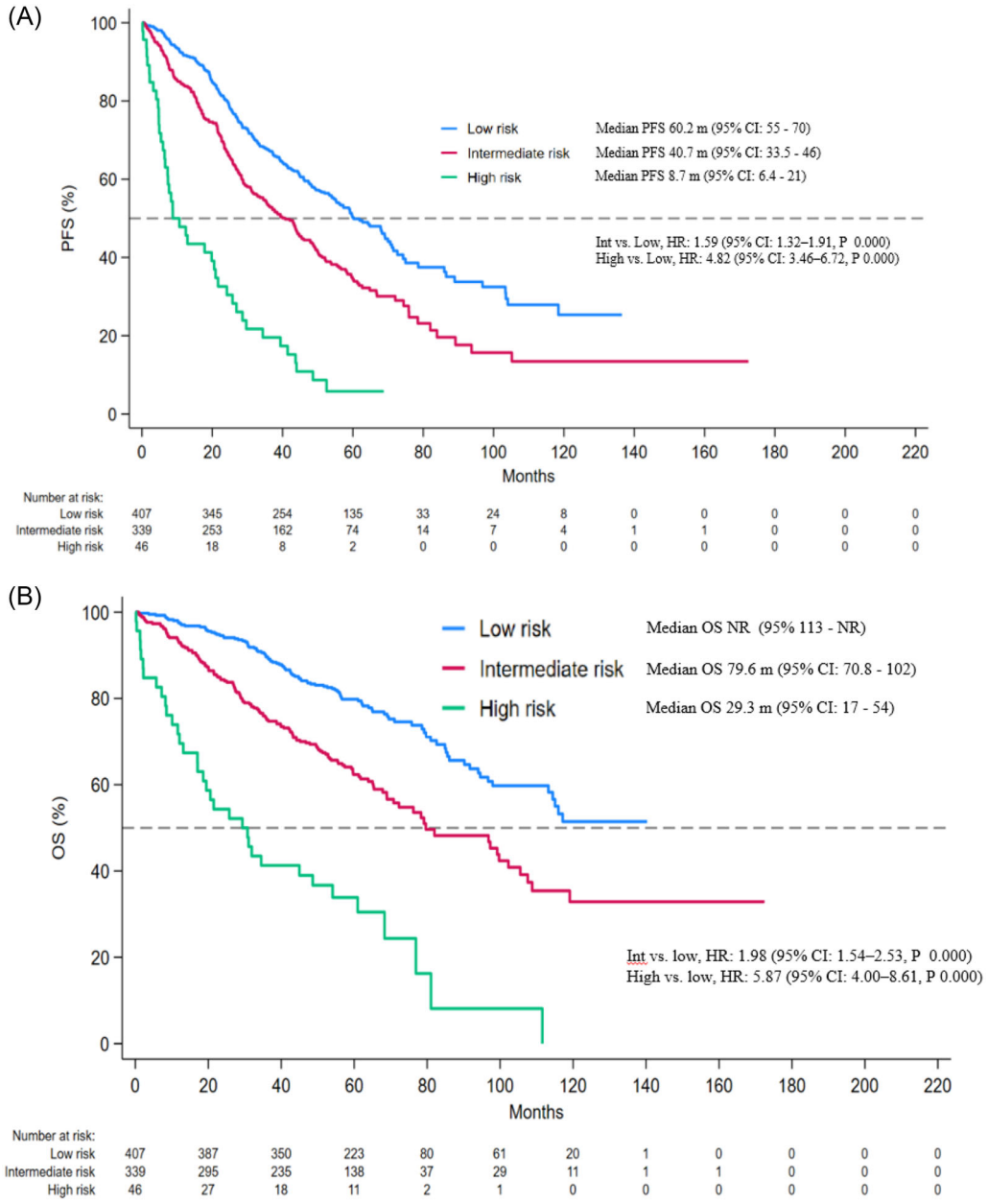

FIGURE 1 **(A) PFS and (B) OS stratified by prognostic score**. B-ERMM, Basal Early Relapse Multiple Myeloma score; CI, confidence interval; High, high risk; HR, hazard ratio; Int, intermediate risk; Low, low risk; m, month; OS, overall survival; PFS, progression-free survival.

transplant-ineligible may become obsolete with newer regimens that are changing the treatment paradigm with independence of chronological age.[5,28,29] Therefore, it would be beneficial to standardize the concept of ER independent of transplantation. ER within 18 months after treatment initiation was proposed by other groups,[17,18] and here we confirmed that ER18 could be a suitable definition in protocols with or without autologous transplant because it is the expected time window to achieve a best response. For this reason, we grouped 1215 transplant candidates and non-candidate patients treated in four clinical trials conducted by the Spanish Myeloma Group (GEM), and used the definition of ER within 18 months after treatment initiation (ER18). We observed that 22% of patients met this criterion, who showed a median OS of only 19 months compared to 114 months in the reference population.

Although prognostic factors in MM are well established, these may not overlap with the factors associated with risk of ER. In accordance with previous studies,[6,8,11,15,30,31] we confirmed that ECOG = 2, ISS 3, elevated LDH, and calcium as well as the presence of HRCA were associated with ER18. In contrast, parameters that were predictive in other studies such as age, sex, or myeloma subtype had no significant association with ER18 in our cohort.[8,31–33] Interestingly, although high tumor burden or aggressive disease biology presenting as high LDH levels may led to poor performance status, ECOG performance status retained independent association with ER18.

The presence of HRCA, particularly the association of two or more that is commonly described as “double hit”, is one of the most important prognostic factors in MM.[34–36] Here, we demonstrate that

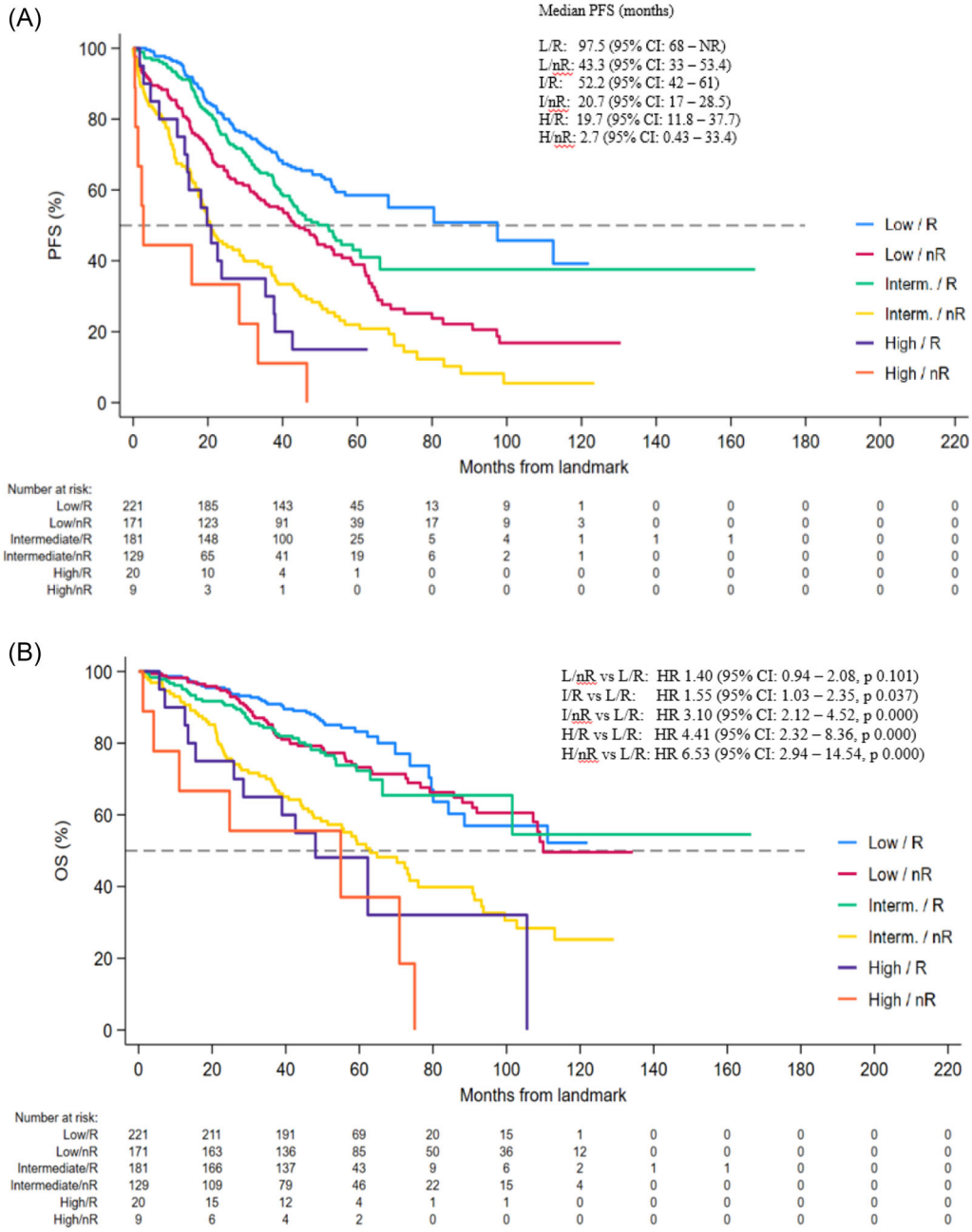

FIGURE 2 **(A) PFS and (B) OS stratified by prognostic score and response to treatment**. L/R versus L/R: HR 1.89 (95% CI 1.44–2.49, $p = 0.000$); L/nR versus L/R: HR 1.89 (95% CI 1.44–2.49, $p = 0.000$); I/R versus L/R: HR 1.49 (95% CI 1.11–1.98, $p = 0.007$); I/nR versus L/R: HR 3.18 (95% CI 2.40–4.22, $p = 0.000$); H/R versus L/R: HR 4.01 (95% CI 2.38–6.75, $p = 0.000$); H/nR versus L/R: HR 7.78 (95% CI 3.91–15.48, $p = 0.000$). CI, confidence interval; High, high risk; HR, hazard ratio; Interm, intermediate risk; Low, low risk; nR, no response; OS, overall survival; PFS, progression-free survival; R, response.

this also applies to the prediction of ER18. Furthermore, we aimed at investigating, for the first time, the association between ER18 and the novel high-risk classification of the IMS (HR-IMS). Interestingly, our results indicate that the association between ER18 and mHR-IMS was stronger than the association with the presence of the del(17p), t(4;14), and/or t(14;16) HRCA, and in fact, it was similar to the association between ER18 and the presence of ≥2 HRCA. Moreover, the concept of double-hit based on the presence of del(17p) plus any other risk category of the mHR-IMS ("double-hit HR-IMS") showed the strongest association with ER18. Although our study has the limitation of lacking data on p53 mutations or biallelic 1p deletions—two genetic abnormalities that require molecular screening—this limitation is mitigated by the fact that most genetic studies in MM continue relying on FISH. Therefore, our mHR-IMS classification can be readily used in ongoing clinical trials and in routine practice lacking molecular data. In line with the strong impact of genetic abnormalities described in our study, Maura et al.[37] have recently developed an individualized risk-prediction model using a more sophisticated molecular characterization that included 20 genomic variables.

Several groups (GIMEMA, EBMT, or CIBMTR)[33,38–40] have developed risk models to predict ER based on baseline features. The variables used in these models are in general agreement with the

parameters that, in our study, showed independent association with a higher risk of ER18: ECOG = 2, ISS 3, calcium ≥ 11 mg/dL, elevated LDH, >60% PC, and the presence of mHR-IMS. Likewise, a very recent study developed among the HARMONY/EMN consortium also identified similar variable associated with ER18.[41] Achieving VGPR or better at 6–9 months after treatment initiation was further confirmed in our study to significantly reduce the risk of ER.[33,38,39] Interestingly, we observed that patients with intermediate-risk of ER18 at baseline achieving ≥VGPR had survival outcomes similar to those with low-risk of ER18 who attained less than VGPR. In line with these results, Zaccaria et al.[33] showed that achieving a ≥VGPR response 9 months after treatment initiation modulated the risk of ER and improved baseline risk stratification. The EBMT included the depth of response at the time of transplant model in the risk model to predict ER. The CIBMTR model included response as percentage of plasma cells in bone marrow <10% or ≥10% at the time of transplant in the risk model.

The positive impact of achieving ≥VGPR was not significant in patients with high-risk of ER18 at baseline. It could be hypothesized that the dismal survival of these patients may only be abrogated, at least in part, with a deeper response such as MRD negativity. In our study, the achievement of MRD negativity after induction was associated with longer PFS among the three high-risk categories.

Our study has several limitations, the main being the lack of validation of the score in an independent cohort of patients. In addition, none of the induction treatments used contained anti-CD38 monoclonal antibodies, which have become standard of care in newly-diagnosed MM.[1–3,28,29,42,43] Thus, it will be paramount to analyze the impact of our baseline and dynamic risk models (i.e., with or without depth of response) in the setting of quadruplet therapy inducing higher rates of MRD negativity and see if this may abrogate the dismal survival of patients with high-risk of ER18. Moreover, CTCs have only been analyzed in a subgroup of patients treated in the GEM2012menos65 trial and given it the prognostic impact it will be of great interest to analyze the role of CTCs in ER18 in a larger and independent cohort of patients. It should be noted that the optimal threshold of CTCs might probably depend on its clinical application. Thus, the identification of patients with very high risk of early disease progression such as ER18, the most informative threshold will necessarily be one log higher than for general prognostication. Finally, in this study, we haven't any functional imaging data available that could also be relevant in identifying ER18.[44–46]

In conclusion, our findings show that the presence of HRCA, particularly the new mHR-IMS classification together with other easily accessible variables such as ISS, calcium, and LDH may help to predict risk of ER18. Because of its significant association with ER18, it is inherently associated with survival outcomes as well. Furthermore, we showed how response to frontline therapy can significantly modify the risk of ER18, which underlies that in patients with high-risk of ER18 the primary goal of treatment should be achieving a deep and durable response.

AUTHOR CONTRIBUTIONS

Andrea Manubens, Jesús F. San Miguel, Bruno Paiva, and Paula Rodriguez-Otero designed the study. Andrea Manubens and Jorge M. Núñez Córdoba did the statistical analysis. Andrea Manubens, Jesús F. San Miguel, Bruno Paiva, Jorge M. Núñez-Córdoba, and Paula Rodriguez-Otero wrote the manuscript. All authors contributed to enrolling patients in the clinical trials and provided the data. All authors reviewed and approved the manuscript.

CONFLICT OF INTEREST STATEMENT

A. M. declares no conflicts of interest. P. R.-O. declares honoraria derived from consulting or advisory board roles with Celgene-BMS, Janssen, Roche, AbbVie, Pfizer, GSK, Sanofi, and H3Biomedicine; steering committee membership with Celgene-BMS, Regeneron, and Janssen; speakers' bureau for Janssen, Celgene-BMS, GSK, Sanofi, and AbbVie; and travel grants from Pfizer. J. S. M. declares honoraria for lectures and participtions on advisory boards from AbbVie, Amgen, BMS, Celgene, F. Hoffman-La Roche, GSK, HaemaLogiX, Janssen-Cilag, Karyopharm, Merck, Novartis, Pfizer, Regeneron, Sanofi-Aventis, Takeda, and SecuraBio. B. P. declares honoraria for lectures from and membership on advisory boards with Adaptive, Amgen, Bristol-Myers Squibb-Celgene, Gilead, GSK, Janssen, Oncopeptides, Roche, Sanofi, Takeda, and The Binding Site; unrestricted grants from Bristol-Myers Squibb-Celgene, EngMab, GSK, Roche, Sanofi, and Takeda; and consultancy for Bristol-Myers Squibb-Celgene, Janssen, and Sanofi. V. C. received honoraria for lectures, consulting, and advisory boards from Johnson & Johnson, BMS, Sanofi, Amgen, Glaxo, Pfizer, BioGene, Menarini; travel grants from Johnson & Johnson, BMS, Amgen, BioGene; speakers' bureau participation for BMS; and financing of scientific research from Janssen. N. C. G. has received honoraria from Janssen, Amgen, and Sanofi. L. R. reports honoraria from Janssen, Celgene, Amgen, and Takeda. A. O. declares consultant activities with Amgen, Celgene, BMS, GSK, Janssen, and Sanofi. J. M.-L. declares honoraria from consulting activities from Astellas Pharma, BMS, F. Hoffman-La Roche, Janssen, Novartis, and Sanofi; and a research grant from BMS. M. V. M. declares honoraria derived from lectures and participation in advisory boards with Johnson & Johnson, Celgene-BMS, Amgen, Takeda, Sanofi, GSK, Pfizer, Kite, Oncopeptides, Stemline-Menarini, Regeneron, and AbbVie. J. d. l. R. declares honoraria derived from lectures and participation in advisory boards with Johnson & Johnson, Celgene-BMS, Takeda, Sanofi, GSK, Pfizer, and Stemline-Menarini. E. M. O. declares honoraria/consulting fees from AbbVie, Amgen, AstraZeneca, BMS, GSK, Janssen, Karyopharm, Menarini, Oncopeptides, Pfizer, Regeneron, Sanofi, and Takeda. M. G. reports consulting fees, honoraria, and participation in advisory boards for J&J, Amgen, Sanofi, Pfizer, and Menarini Stemline. F. d. A. declares honoraria derived from lectures and participation in advisory boards with Johnson & Johnson, Celgene-BMS, Amgen, GSK, Sanofi, and Takeda. J. B. declares honoraria for lectures from Janssen, Celgene/BMS, Amgen, and Sanofi. J. M. A. declares honoraria for lectures and advisory boards from Johnson & Johnson, Sanofi, GSK, Amgen, Roche, Bristol-Myers Squibb, and BindingSite. A. A. declares honoraria derived from lectures and participation in advisory boards with Amgen, Johnson & Johnson, Celgene-BMS, Sanofi, Pfizer, Oncopeptides, GSK, and Regeneron. J. J. L. declares consulting or advisory roles with Celgene, Amgen, Janssen-Cilag, and Sanofi; and travel, accommodations, and expenses were provided by Celgene and Pfizer. The remaining authors declare no competing interests relative to this work.

DATA AVAILABILITY STATEMENT

The Spanish Myeloma Group is open to the possibility of sharing the data used in this study for research projects as long as they do not interfere with the present or future objectives of the clinical trial. The interest and feasibility of any clinical or biological research proposal based on the data from this study must be approved by the board of directors of the Spanish Myeloma Group. In such a case, the data, deposited in REDCap, will be presented in anonymized CSV format. This availability is subject to the laws and provisions in force that regulate the development of clinical trials both in Spain and in the European Union. Data are available on request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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