original reports

Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within the HARMONY Project

Mattia D'Agostino, MD[1]; David A. Cairns, PhD[2]; Juan José Lahuerta, MD, PhD[3]; Ruth Wester, MD[4]; Uta Bertsch, MD[5]; Anders Waage, MD, PhD[6]; Elena Zamagni, MD, PhD[7,8]; María-Victoria Mateos, MD, PhD[9]; Daniele Dall'Olio, MSc[10]; Niels W.C.J. van de Donk, MD, PhD[11]; Graham Jackson, MD[12]; Serena Rocchi, MD[7,8]; Hans Salwender, MD[13]; Joan Bladé Creixenti, MD, PhD[14]; Bronno van der Holt, PhD[15]; Gastone Castellani, PhD[8]; Francesca Bonello, MD[1]; Andrea Capra, MScEng[1]; Elias K. Mai, MD[5]; Jan Dürig, MD[16]; Francesca Gay, MD, PhD[1]; Sonja Zweegman, MD, PhD[11]; Michele Cavo, MD[7,8]; Martin F. Kaiser, MD[17]; Hartmut Goldschmidt, MD[5]; Jesús María Hernández Rivas, MD, PhD[18]; Alessandra Larocca, MD, PhD[1]; Gordon Cook, MD, PhD[2]; Jesús F. San-Miguel, MD, PhD[19]; Mario Boccadoro, MD[1]; and Pieter Sonneveld, MD, PhD[4]

abstract

PURPOSE Patients with newly diagnosed multiple myeloma (NDMM) show heterogeneous outcomes, and approximately 60% of them are at intermediate-risk according to the Revised International Staging system (R-ISS), the standard-of-care risk stratification model. Moreover, chromosome 1q gain/amplification (1q+) recently proved to be a poor prognostic factor. In this study, we revised the R-ISS by analyzing the additive value of each single risk feature, including 1q+.

PATIENTS AND METHODS The European Myeloma Network, within the HARMONY project, collected individual data from 10,843 patients with NDMM enrolled in 16 clinical trials. An additive scoring system on the basis of top features predicting progression-free survival (PFS) and overall survival (OS) was developed and validated.

RESULTS In the training set (N = 7,072), at a median follow-up of 75 months, ISS, del(17p), lactate dehydrogenase, t(4;14), and 1q+ had the highest impact on PFS and OS. These variables were all simultaneously present in 2,226 patients. A value was assigned to each risk feature according to their OS impact (ISS-III 1.5, ISS-II 1, del(17p) 1, high lactate dehydrogenase 1, and 1q+ 0.5 points). Patients were stratified into four risk groups according to the total additive score: low (Second Revision of the International Staging System [R2-ISS]-I, 19.2%, 0 points), low-intermediate (II, 30.8%, 0.5-1 points), intermediate-high (III, 41.2%, 1.5-2.5 points), high (IV, 8.8%, 3-5 points). Median OS was not reached versus 109.2 versus 68.5 versus 37.9 months, and median PFS was 68 versus 45.5 versus 30.2 versus 19.9 months, respectively. The score was validated in an independent validation set (N = 3,771, of whom 1,214 were with complete data to calculate R2-ISS) maintaining its prognostic value.

CONCLUSION The R2-ISS is a simple prognostic staging system allowing a better stratification of patients with intermediate-risk NDMM. The additive nature of this score fosters its future implementation with new prognostic variables.

J Clin Oncol 00. © 2022 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on April 8, 2022 and published at ascopubs.org/journal/jco on May 23, 2022: DOI https://doi.org/10.1200/JCO.21.02614

INTRODUCTION

Multiple myeloma (MM) is a hematologic disease with heterogeneous outcomes and is associated with survival rates ranging from few months to more than a decade.[1] In 2015, the Revised International Staging System (R-ISS) was introduced to develop a robust prognostic system on the basis of widely available biomarkers, and is now considered a standard risk stratification model for patients with newly diagnosed multiple myeloma (NDMM).[2,3]

The R-ISS takes into account ISS (which integrates β2-microglobulin levels and serum albumin to reflect tumor mass and renal function),[4] high-risk chromosomal abnormalities (CA) detected by interphase fluorescence in situ hybridization (FISH) [deletion(17p), translocation t(4;14)(p16;q32), or t(14;16)(q32;q23)],[5] and serum lactate dehydrogenase (LDH) levels.[6,7] The R-ISS identifies three groups: R-ISS I including ISS I without neither high-risk CA nor high LDH levels; R-ISS III including ISS III and either high-risk CA or high LDH levels; and R-ISS II including all the other possible combinations. At a median follow-up of 46 months, median overall survival (OS) was not reached (NR) in

CONTEXT

Key Objective

The European Myeloma Network, within the HARMONY project, collected data from 10,843 patients with newly diagnosed multiple myeloma to propose a second revision (R2-ISS) of the current Revised International Staging System (R-ISS; Palumbo et al, 2015). The top features predicting overall survival (OS) and progression-free survival, including 1q gain/amplification (1q+), were used to develop and validate an additive risk score.

Knowledge Generated

The impact on OS of ISS, del(17p), lactate dehydrogenase, t(4;14), and 1q+ was used to define R2-ISS. Four risk groups predicting different OS and progression-free survival rates were identified: low (R2-ISS-I, 19.2%), low-intermediate (II, 30.8%), intermediate-high (III, 41.2%), high (IV, 8.8%).

Relevance (*S. Lentzsch*)

Compared with the R-ISS, the R2-ISS is an improved and simple staging system that includes the independent poor prognostic factors 1q gain (three copies of 1q) or amplification (≥ four copies of 1q) resulting in better stratification of especially the large group of patients with intermediate-risk newly diagnosed multiple myeloma.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

the R-ISS I group, 83 months in the R-ISS II group, and 43 in the R-ISS III group, respectively.[2]

The main limitation of the R-ISS was that 62% of patients were classified into the intermediate-risk category (R-ISS II), possibly including patients with different risk levels of progression/death.

Recently, 1q gain (three copies of 1q) or amplification (≥ four copies of 1q), which were not included in the R-ISS, proved to be independent poor prognostic factors in NDMM.[8-10] Moreover, in the R-ISS, high-risk CA were considered as present if at least one among del(17p), t(4;14), or t(14;16) was detected, whereas emerging data showed that having more than one high-risk CA predicted poorer outcomes.[8]

The European Myeloma Network (EMN), under the umbrella of the European Union–funded HARMONY project,[11] collected individual patient data from a large cohort of young and elderly patients with NDMM to improve risk stratification and propose a revision of the current R-ISS, which is here referred to as the Second Revision of the ISS (R2-ISS). In this work, we analyzed the prognostic value of each single baseline risk feature in an additive fashion, including 1q gain/amplification in the risk calculation.

PATIENTS AND METHODS

Patients

In this analysis, we included 10,843 patients with NDMM who were enrolled in 16 international, multicenter clinical trials from 2005 to 2016 and met the data quality requirements (Data Supplement [online only], Supplementary methods, Table S1). The results of the included trials were previously reported (IST-CAR-506,[12] EMN01,[13,14] RV-MM-EMN-441,[15] MM-RV-PI-209,[16] RV-MM-PI-114,[17,18] GIMEMA-MM-03-05,[19,20] 26866138MMY2069,[21] HOVON-65/GMMG-HD4,[22,23] MM-BO2005,[24,25] GEM05MENOS65,[26,27] EMN02/HO95,[28,29] GEM05MAS65,[30-32] GEM2010MAS65,[33] HOVON-87/NMSG-18,[34] GMMG-MM5,[35,36] and UK National Cancer Research Institute [UK NCRI] Myeloma XI[37-41]). Written informed consent was provided before entering the source trials, which were approved by the institutional review boards and ethics committees at each of the participating centers and conducted in accordance with the Declaration of Helsinki. After the acquisition of data from the source trials, all patient data were de facto anonymized[42] in compliance with the General Data Protection Regulation, harmonized and transformed using an Observational Medical Outcomes Partnership Common Data Model,[43] and eventually registered in the HARMONY Big Data Platform.

During their upfront treatment, all patients received at least an immunomodulatory drug (IMiD) and/or a proteasome inhibitor (PI) during the induction or consolidation/maintenance phases (Data Supplement Table S2).

The collected baseline data and the definition of each variable are available in the Data Supplement.

OS was the primary end point and was defined as the time from symptomatic MM diagnosis until death due to any cause, or until the last date the patient was known to be alive. Progression-free survival (PFS) was the secondary end point and was defined as the time from symptomatic MM diagnosis until progression or death due to any cause, or until the last date the patient was known to be alive and free of progression.

CA Detection

Bone marrow plasma cells were enriched using a CD138-directed enrichment, and CD138+ bone marrow plasma cells were analyzed by FISH as previously described[2,9] (in the training set) or by molecular methods validated against FISH[8] (in the validation set; see the Data Supplement). Data about the presence of the following CA were acquired at

baseline: del(17p), gain/amp(1q21), t(4;14)(p16;q32), and t(14;16)(q32;q23). Since data about the number of nuclei with three (gain) or ≥ four (amp) copies of 1q21 were not available, gain or amp(1q21) were grouped together regardless of copy numbers of the gained region and were indicated with the symbol 1q+.[44]

Patients were considered positive for each CA when its percentage was higher than a cutoff threshold defined by each local laboratory. Details about cutoff variability among laboratories are reported in the Data Supplement.

Statistical Analysis

Patients were analyzed on an intention-to-treat basis.

The patient population was divided into a training set (7,072 patients enrolled in 15 clinical trials) and a validation set (3,771 patients treated in the UK NCRI Myeloma XI trial; Table 1). The UK NCRI Myeloma XI trial was included in the HARMONY Big Data Platform as an external validation set on June 23, 2021, when the training set[45] had already been developed. The UK NCRI Myeloma XI enrolled both transplant-eligible (TE) and transplant-ineligible (NTE) patients (Data Supplement).

OS and PFS were estimated by using the Kaplan-Meier method and analyzed with the Cox proportional hazards model (Fig 1), which was adjusted for age (1-year increase), sex (M *v* F), transplant eligibility (TE *v* NTE), and type of treatment (PIs *v* IMiDs *v* PIs plus IMiDs).

The features with the highest impact on OS and PFS were further evaluated to build an additive score.

An IPCW (inverse probability of censoring weighted) method was used to compute the C-index estimates.[46] The discrimination ability of a model including ≥ 1 variables was evaluated using the C-index estimates (Data Supplement Fig S1). After the inclusion of the top five predictors, the sixth predictor had a significant effect on OS, but it was not significant in terms of PFS (Fig 1). Moreover, the C-index estimate for OS did not substantially improve with six compared with five predictors (Data Supplement Fig S1). Thus, the top five features with the most significant impact on OS and PFS were used to build the score.

A Cox proportional hazards model was performed in cases that were complete for all the significant prognostic features (n = 2,226).

A score value was assigned to each predictor and was computed as the ratio between the coefficient of the Cox model,[47] using OS as outcome (Table 2), and the coefficient related to the comparison ISS II versus ISS I. The coefficient related to the comparison ISS II versus ISS I was used as the reference value (score value = 1). The score values assigned to the predictors were calculated and rounded to the nearest 0.5. The Kaplan-Meier curves for OS defined according to each 0.5 score point of the additive score and the grouping strategy are shown in the Data Supplement (Fig S2). The definition of the cutoffs used to divide the population into four risk-defined groups is described in the Data Supplement (Supplementary methods and Table S3).

Group differences according to the final R2-ISS classification were investigated using the Cox proportional hazards model for OS and PFS in the training and validation sets.

A log-negative log plot by R2-ISS risk group for OS was performed (Data Supplement Fig S3) as a visual approach to evaluate the proportional hazards assumption.

All reported *P* values are two-sided at the conventional 5% significance level. Data were analyzed as of September 10, 2021, using R software (v3.6.3).

RESULTS

Patient Characteristics and Treatments

In the training set (N = 7,072 patients), the median age was 62 years (range, 18-91 years); 62% of patients were age ≤ 65 and 38% were age > 65 years. A total of 65% of patients were TE and 35% were NTE. During their first line of treatment, 40% of patients received an IMiD-based therapy, 15% a PI, and 46% both an IMiD and a PI. The median follow-up was 75.5 months.

In the validation set (N = 3,771 patients), the median age was 68 years (interquartile range, 60-74 years); 42% of patients were age ≤ 65 years and 58% were age > 65 years. A total of 53% of patients were TE and 47% NTE. During their first line of treatment, 89% of patients received an IMiD-based therapy and 11% both an IMiD and a PI. The median follow-up was 60 months.

Feature Selection

The individual role of each predictor was evaluated in the total population of the training set. Baseline characteristics are described in Table 1, and the impact of each predictor on OS and PFS is described in Figure 1.

The statistically significant predictors for OS in multivariate analysis were ISS stage (hazard ratio [HR], 2.03 [95% CI, 1.83 to 2.25] for ISS III *v* I and HR, 1.55 [95% CI, 1.42 to 1.69] for ISS II *v* I); del(17p) (HR, 1.74 [95% CI, 1.56 to 1.94] *v* no del(17p)); LDH > upper limit of normal ([ULN]; HR 1.66 [95% CI, 1.50 to 1.83] *v* LDH ≤ ULN); t(4;14) (HR 1.56 [95% CI, 1.40 to 1.74] *v* no t(4;14)); 1q+ (HR, 1.45 [95% CI, 1.29 to 1.63] *v* no 1q+); t(14;16) (HR, 1.34 [95% CI, 1.09 to 1.65] *v* no t(14;16)); Eastern Cooperative Oncology Group performance status (ECOG PS) > 1 (HR, 1.32 [95% CI, 1.20 to 1.44] *v* ECOG PS ≤ 1); immunoglobulin A (IgA) heavy chain (HR, 1.23 [95% CI, 1.14 to 1.34] *v* no IgA); and creatinine clearance ≤ 45 mL/min (HR, 1.11 [95% CI, 1.01 to 1.23] *v* creatinine clearance > 45 mL/min).

The statistically significant predictors for PFS in multivariate analysis were ISS stage (HR, 1.53 [95% CI, 1.42 to 1.66] for

TABLE 1. Patient Characteristics and Treatments

Whole Study Population (N = 10,843)	Training Set		Validation Set	
	Total (N = 7,072)	Evaluable for Score Calculation (n = 2,226)	Total (N = 3,771)	Evaluable for Score Calculation (n = 1,214)
Age, years				
Median (IQR)	62 (55-70)	60 (54-65)	68 (60-74)	68 (60.25-74)
≤ 65, No. (%)	4,397 (62)	1,720 (77)	1,575 (42)	495 (41)
> 65, No. (%)	2,675 (38)	506 (23)	2,196 (58)	719 (59)
Sex, No. (%)				
Female	3,216 (45)	955 (43)	1,567 (42)	482 (40)
Male	3,856 (55)	1,271 (57)	2,204 (58)	732 (60)
ISS, No. (%)				
I	2,461 (36)	830 (37)	895 (26)	276 (23)
II	2,724 (40)	845 (38)	1,472 (42)	554 (46)
III	1,689 (25)	551 (25)	1,118 (32)	384 (32)
Missing	198	—	286	—
LDH, No. (%)				
≤ ULN	5,557 (86)	1,863 (84)	2,017 (68)	838 (69)
> ULN	877 (14)	363 (16)	933 (32)	376 (31)
Missing	638	—	821	—
del(17p), No. (%)				
No	4,990 (89)	1,968 (88)	1,424 (91)	1,105 (91)
Yes	633 (11)	258 (12)	135 (9)	109 (9)
Missing	1,449	—	2,212	—
t(4;14), No. (%)				
No	4,750 (87)	1,949 (88)	1,381 (89)	1,080 (89)
Yes	709 (13)	277 (12)	178 (11)	134 (11)
Missing	1,613	—	2,212	—
1q+, No. (%)				
No	1,767 (64)	1,406 (63)	1,034 (66)	815 (67)
Yes	1,003 (36)	820 (37)	525 (34)	399 (33)
Missing	4,302	—	2,212	—
Treatment, No. (%)				
IMiDs	2,825 (40)	506 (23)	3,358 (89)	1,054 (87)
IMiDs-PIs	3,221 (46)	1,485 (67)	413 (11)	160 (13)
PIs	1,026 (15)	235 (11)	—	—
ASCT eligibility, No. (%)				
NTE	2,500 (35)	371 (17)	1,781 (47)	575 (47)
TE	4,572 (65)	1,855 (83)	1,990 (53)	639 (53)

Abbreviations: 1q+, 1q gain/amplification; ASCT, autologous stem-cell transplantation; del, deletion; IMiDs, immunomodulatory drugs; IQR, interquartile range; ISS, International Staging System; LDH, lactate dehydrogenase; NTE, non–transplant-eligible; PIs, proteasome inhibitors; t, translocation; TE, transplant-eligible; ULN, upper limit of normal.

ISS III *v* I and HR, 1.35 [95% CI, 1.26 to 1.44] for ISS II *v* I); del(17p) (HR, 1.41 [95% CI, 1.29 to 1.55] *v* no del(17p)); LDH > ULN (HR, 1.33 [95% CI, 1.23 to 1.45] *v* LDH ≤ ULN); t(4;14) (HR, 1.49 [95% CI, 1.37 to 1.63] *v* no t(4;14)); 1q+ (HR, 1.37 [95% CI, 1.25 to 1.50] *v* no 1q+); ECOG PS > 1 (HR, 1.16 [95% CI, 1.08 to 1.25] *v* ECOG PS ≤ 1); IgA heavy chain (HR, 1.10 [95% CI, 1.03 to 1.17] *v* no IgA); and creatinine clearance ≤ 45 mL/min (HR, 1.11 [95% CI, 1.02 to 1.20] *v* creatinine clearance > 45 mL/min).

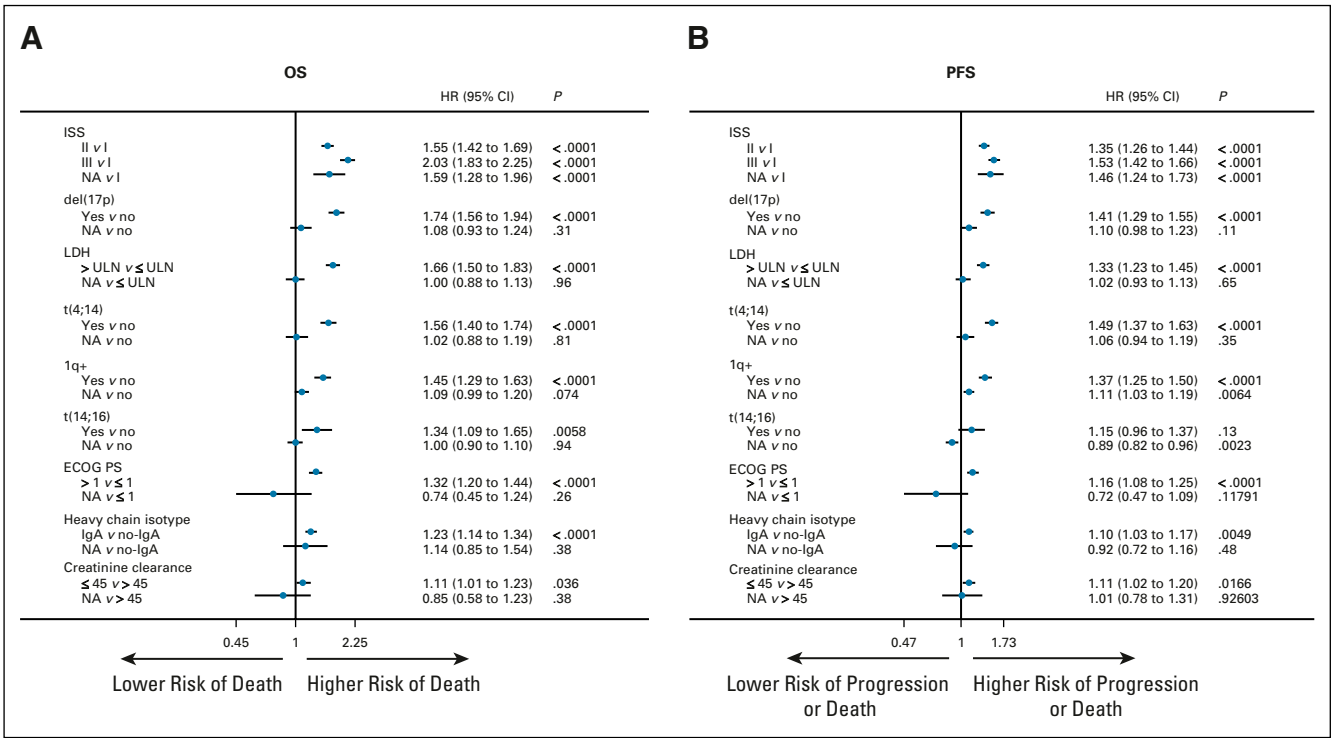


FIG 1. Feature selection: (A) OS impact of the single variables in a multivariate Cox model and (B) PFS impact of the single variables in a multivariate Cox model. N = 7,072 patients (training set). 1q+, 1q gain/amplification; del, deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IgA, immunoglobulin A; ISS, International Staging System; LDH, lactate dehydrogenase; NA, not available; OS, overall survival; PFS, progression-free survival; t, translocation; ULN, upper limit of normal.

Of note, t(14;16)-positive patients showed only a trend toward a shorter PFS in multivariate analysis, but it was not significant (HR, 1.15 [95% CI, 0.96 to 1.37] *v* no t(14;16), $P = .13$).

Score Calculation

The top predictors significantly affecting both OS and PFS (ISS, del(17p), LDH, t(4;14), and 1q+) were used to build an additive score. In the training set, data on 2,226 patients

TABLE 2. R2-ISS Score Definition on the Basis of the Evaluable Patients Included in the Training Set (n = 2,226)

Risk Feature	OS HR (95% CI)	PFS HR (95% CI)	Score Value[a]
ISS II	1.75 (1.49 to 2.05)	1.43 (1.28 to 1.61)	1
ISS III	2.53 (2.13 to 3.01)	1.76 (1.54 to 2.01)	1.5
del(17p)	1.82 (1.53 to 2.17)	1.43 (1.23 to 1.65)	1
LDH high	1.60 (1.36 to 1.88)	1.37 (1.20 to 1.57)	1
t(4;14)	1.53 (1.29 to 1.81)	1.40 (1.21 to 1.62)	1
1q+	1.47 (1.29 to 1.68)	1.33 (1.20 to 1.48)	0.5

Group	No. (%)	Total Additive Score
Low (I)	428 (19)	0
Low-intermediate (II)	686 (31)	0.5-1
Intermediate-high (III)	917 (41)	1.5-2.5
High (IV)	195 (9)	3-5

Abbreviations: 1q+, 1q gain/amplification; del, deletion; HR, hazard ratio; ISS, International Staging System; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; R2-ISS, Second Revision of the ISS; t, translocation.

[a]Score values were calculated using OS as outcome and were rounded to the nearest 0.5. The coefficient related to the comparison ISS II versus I was used as the reference value (score value = 1).

were complete for all significant risk factors (Table 1). Four groups were identified according to the additive score: low risk (R2-ISS I, 0 points), low-intermediate risk (R2-ISS II, 0.5-1 points), intermediate-high risk (R2-ISS III, 1.5-2.5 points), and high risk (R2-ISS IV, 3-5 points). The distribution of the single risk features within each R2-ISS group is shown in Table 3.

In the training set, R2-ISS I patients were 428 (19.2%), R2-ISS II 686 (30.8%), R2-ISS III 917 (41.2%), and R2-ISS IV 195 (8.8%). Median OS was NR (95% CI, NR to NR) versus 109.2 (95% CI, 99.5 to NR) versus 68.5 (95% CI, 63.9 to 73.9) versus 37.9 (95% CI, 32.7 to 46.3) months, with a 5-year OS rate of 88% (95% CI, 84% to 91%) versus 75% (95% CI, 71% to 78%) versus 56% (95% CI, 53% to 59%) versus 37% (95% CI, 31% to 45%) in the R2-ISS I, II, III, and IV groups, respectively. Median PFS was 68 (95% CI, 60.5 to 85.3) versus 45.5 (95% CI, 42.3 to 50.3) versus 30.2 (95% CI, 27.5 to 32.6) versus 19.9 (95% CI, 17.4 to 23.5) months, with a 5-year PFS rate of 55% (95% CI, 51% to 60%) versus 40% (95% CI, 36% to 44%) versus 25% (95% CI, 22% to 28%) versus 17% (95% CI, 12% to 23%), respectively. The differences among the R2-ISS groups were statistically significant (Figs 2A and 2C).

The performance of the R2-ISS on OS in different subgroups of patients was explored. The R2-ISS maintained its discriminating ability in TE, NTE, IMiD-treated, PI-treated, and IMiD plus PI-treated patients (Fig 3). The R2-ISS performance in terms of PFS in the same subgroups is shown in the Data Supplement (Fig S4).

In the validation set, the predictors defining the score were simultaneously present in 1,214 patients (Table 1). R2-ISS I patients were 135 (11.1%), R2-ISS II 322 (26.5%), R2-ISS III 627 (51.6%), and R2-ISS IV 130 (10.7%). Median OS was NR (95% CI, 84.7 to NR) versus 88.8 (95% CI, 78.2 to NR) versus 56.2 (95% CI, 50 to 61.9) versus 33.9 (95% CI, 27.7 to 40.4) months, with a 5-year OS rate of 80% (95% CI, 73% to 88%) versus 70% (95% CI, 64% to 75%) versus 48% (95% CI, 44% to 52%) versus 24% (95% CI, 17% to 33%) in the R2-ISS I, II, III, and IV groups, respectively. Median PFS was 39.3 (95% CI, 32.4 to 49.7) versus 28 (95% CI, 24.7 to 32.5) versus 19.4 (95% CI, 17.9 to 21.9) versus 14.9 (95% CI, 12.1 to 16.4) months, with a 5-year PFS rate of 34% (95% CI, 26% to 43%) versus 26% (95% CI, 21% to 32%) versus 16% (95% CI, 13% to 19%) versus 10% (95% CI, 6% to 17%), respectively. The differences among the R2-ISS groups were statistically significant (Figs 2B and 2D).

OS discrimination and OS calibration of the R2-ISS are detailed in the Data Supplement (Table S4 and Fig S5).

Comparison Between R2-ISS and R-ISS

We were interested in identifying how many R-ISS patients were redistributed with the new R2-ISS scoring system and how the R-ISS compared with the R2-ISS. Table S5 in the Data Supplement shows the redistribution of patients originally classified according to the R-ISS with the new R2-ISS risk score, and Figure S6 in the Data Supplement shows the survival curves according to R2-ISS and R-ISS groups in the same patient population.

One of the aims of this study was to better discriminate the survival in the large group of R-ISS II patients. We therefore evaluated OS in R-ISS II patients according to the new R2-ISS score (Data Supplement Fig S7). Of note, within the R-ISS II patients in the training set, median OS was 111 months in R2-ISS II, 71 months in R2-ISS III, and 57 months in the R2-ISS IV patients**.** Within the R-ISS II patients in the validation set, median OS was 89 months in R2-ISS II, 56 months in R2-ISS III, and 27 months in the R2-ISS IV patients. These differences were statistically significant (Data Supplement Figs S7a and S7c), thus confirming that R-ISS II patients represent a very heterogeneous population in terms of survival that can be discriminated through the R2-ISS. The same analysis on PFS is shown in Figures S7b and S7d in the Data Supplement.

DISCUSSION

In this study, widely available prognostic tools such as ISS, LDH levels, and CA identified by FISH (del(17p), t(4;14), and 1q+) were combined to define an additive score to stratify

TABLE 3. ISS, LDH, del(17p), t(4;14), and 1q+ Distribution According to the R2-ISS in Evaluable Patients Included in the Training Set (n = 2,226)

R2-ISS Risk Group	R2-ISS Low (I, n = 428), No. (%)	R2-ISS Low-Intermediate (II, n = 686), No. (%)	R2-ISS Intermediate-High (III, n = 917), No. (%)	R2-ISS High (IV, n = 195), No. (%)
No risk factors	428 (100)	—	—	—
ISS II	—	396 (58)	407 (44)	42 (22)
ISS III	—	—	400 (44)	151 (77)
LDH	—	55 (8)	186 (20)	122 (63)
del(17p)	—	45 (7)	132 (14)	81 (42)
t(4;14)	—	21 (3)	159 (17)	97 (50)
1q+	—	169 (25)	498 (54)	153 (78)

Abbreviations: 1q+, 1q gain/amplification; del, deletion; ISS, International Staging System; LDH, lactate dehydrogenase; R2-ISS, Second Revision of the ISS; t, translocation.

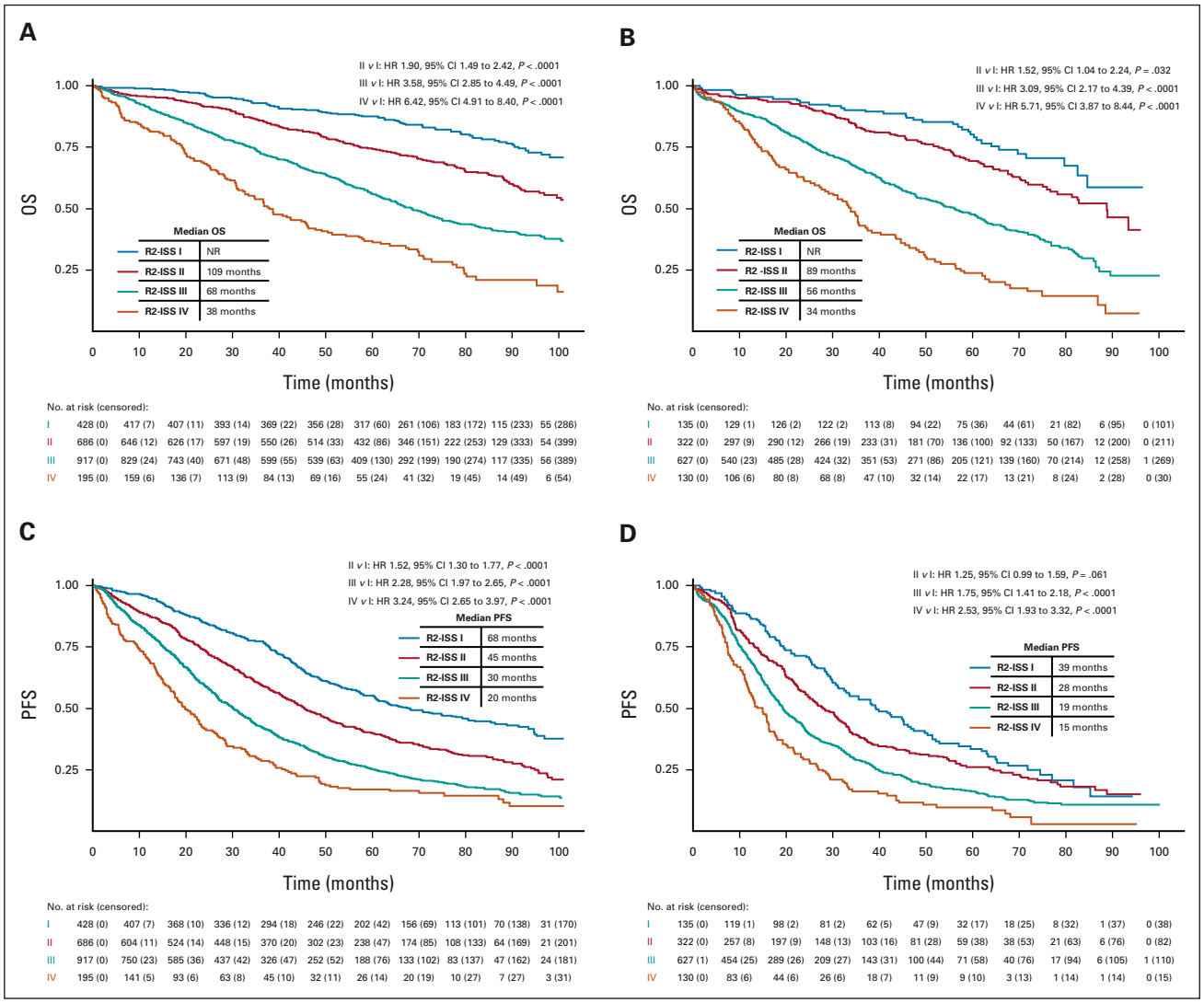


FIG 2. Survival outcomes in patients with multiple myeloma stratified by the R2-ISS algorithm: (A) OS in the training set, (B) OS in the validation set, (C) PFS in the training set, and (D) PFS in the validation set. HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival; R2-ISS, Second Revision of the International Staging System.

patients with NDMM. Compared with the R-ISS,[2] the R2-ISS adds 1q+ to the score, and its calculation takes into account the prognostic significance of the coexistence of several CA.

Of note, 1q+ is a very common finding in NDMM, with approximately 40% of patients presenting with this abnormality.[44] Although this variable was missing in many older trials included in this analysis, the multivariate analysis on the available patients (2,770 patients in the training cohort only) clearly confirmed its prognostic role in patients with NDMM.

In the analysis of CA in the validation set, a certain proportion of missing cases was also observed, although the missingness mechanism was different from that in the training set. Indeed, CA analysis in the validation set required a centralized sample that was not mandatory, and a lower-than-expected sample compliance was registered. However, complete cases were enough to validate our score, and the OS in complete versus incomplete cases was similar (Data Supplement Fig S8), thus revealing no evidence of selection bias.

In our analysis, t(14;16), which was included in the R-ISS, was significant in terms of OS but not of PFS and, as a consequence, was not included in the R2-ISS calculation. Indeed, despite its biological importance, t(14;16) is rare and usually presents together with other adverse prognostic factors.[48,49] Moreover, it may not be a marker of high-risk disease per se, as observed here and by other groups analyzing large cohorts of patients.[48,49]

Compared with the R-ISS, the R2-ISS has the advantage of being validated in an independent cohort of patients. Furthermore, a longer follow-up in this study (75.5 months *v* 46 months in the R-ISS study)[2] allowed us to analyze more precisely the OS of our patient cohort.

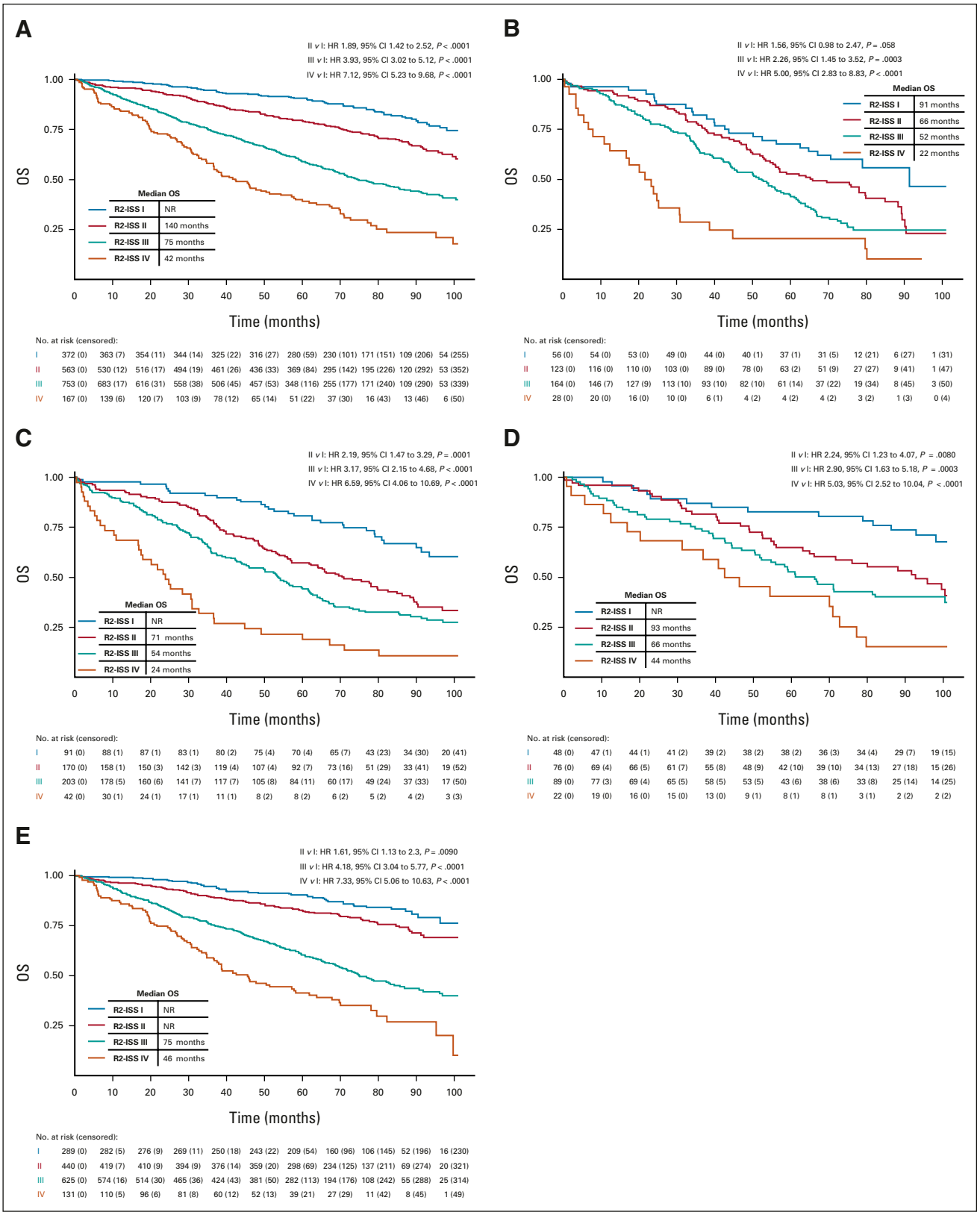


FIG 3. R2-ISS and OS by transplant eligibility and type of treatment in the training set: (A) OS in transplant-eligible patients, (B) OS in transplant-ineligible patients, (C) OS in patients receiving regimens based on IMiDs, (D) OS in patients receiving regimens based on PIs, and (E) OS in patients receiving regimens based on IMiDs plus PIs. HR, hazard ratio; IMiDs, immunomodulatory drugs; NR, not reached; OS, overall survival; PIs, proteasome inhibitors; R2-ISS, Second Revision of the International Staging System.

The additive nature of the R2-ISS score calculation allowed us to identify four well-separated groups of patients, rather than the three R-ISS categories. Of note, R2-ISS I (19.2%) plus II (30.8%) patients accounted for 50% of the entire population with NDMM, whereas III (41.2%) plus IV (8.8%) patients for the remaining 50%. This is important because, with the R-ISS, the low- or high-risk populations were usually too small to perform subgroup analyses in trials without large numbers of patients. With the R2-ISS, the NDMM population can be split in half (I-II *v* III-IV) to develop subgroup analyses and potentially design risk-adapted approaches in a substantial number of patients.

A limitation of our study is that TE patients, especially in the training set, are more represented than NTE patients, although the R2-ISS identifies four separate prognostic groups in NTE patients as well. However, in the NTE population, besides disease-specific biomarkers, patient-specific biomarkers are very important,[50] and the validated scores to define patient frailty should be explored in combination with the R2-ISS.[50]

The need for a long-term follow-up to develop a prognostic model affecting OS precluded us from validating the R2-ISS in patients treated with new treatment combinations (eg, carfilzomib-containing regimens,[51] and triplets and quadruplets including monoclonal antibodies[52-54]). However, the validation of the R2-ISS in this patient population should be pursued as soon as the follow-up is mature enough.

The R2-ISS score was entirely developed and validated in a population of patients with NDMM enrolled in clinical trials. In the future, the R2-ISS validation in a real-world population should be pursued. The applicability of the R2-ISS in clinical practice should also be tested, since complete data about all the included variables are needed to calculate the score. Nonetheless, ISS (which is based on albumin and β2-microglobulin levels) and LDH are easily obtainable and widely available parameters, and del(17p), t(4;14), and 1q+ can be simultaneously obtained by FISH from a single bone marrow aspirate. FISH is indeed a standard procedure to be performed at MM diagnosis, and del(17p), t(4;14), and 1q+ are included in the recommended standard FISH panel.[55] As shown in the validation set, if molecular biology techniques validated against FISH are available, they can be used to calculate the R2-ISS as well.

Compared with the R-ISS, the R2-ISS has the advantage of being a flexible additive score that can be easily updated with new prognostic factors as they emerge in the MM field. Interestingly, many other factors not analyzed in this work (eg, circulating plasma cells,[56,57] TP53 mutations,[58,59] 1p32 deletion,[60] lambda light-chain translocations,[61] extramedullary disease,[62,63] and Myc deregulation[64]) were independently associated with a dismal outcome and may potentially be included in the risk stratification strategy at baseline. Additionally, the discrimination among 1q+ cases of gain(1q) (three copies of 1q) versus amp(1q) (≥ four copies of 1q) may further improve the risk stratification.[58,65,66]

Moreover, molecular data (next-generation sequencing[58,59] and/or gene-expression profiling)[67] with a potential prognostic impact were not taken into account in the risk calculation either.

A long-term follow-up and an analysis of these prognostic factors, uniformly evaluated in a large cohort of patients, are needed to conceivably improve the current prognostic score. Moreover, we should understand whether the interaction among these risk factors could not be merely additive, but also synergistic in predicting poor prognosis.

The combination of R2-ISS and response evaluated during treatment by very sensitive techniques (eg, minimal residual disease [MRD] inside and outside the bone marrow) should also be explored. Indeed, the achievement of MRD negativity, assessed at high sensitivity, demonstrated to overcome the poor prognosis conferred by baseline prognostic risk factors.[68] By combining R2-ISS and MRD, the design of risk-adapted plus MRD-adapted strategies can be pursued in a substantial number of patients with NDMM.

As it was done for the R-ISS,[69] the value of the R2-ISS score in a population of patients with relapsed and/or refractory MM should also be explored, to verify whether this score could be used to stratify patients in trials enrolling patients after first-line treatment.

In conclusion, the R2-ISS staging system is a new simple prognostic algorithm. Compared with the R-ISS, it showed an improved discriminating capability, especially in the large group of patients with intermediate-risk NDMM. The R2-ISS score includes simple and widely used prognostic markers, and the additive nature of its calculation easily allows the future inclusion of new prognostic variables.

AFFILIATIONS

[1]SSD Clinical Trial in Oncoematologia e Mieloma Multiplo, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
[2]Leeds Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom
[3]Instituto de Investigación del Hospital Universitario 12 de Octubre, Madrid, Spain
[4]Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands
[5]University Hospital Heidelberg, Internal Medicine V and National Center for Tumor Diseases (NCT), Heidelberg, Germany
[6]Institute of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[7]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli," Bologna, Italy

[8]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy
[9]Complejo Asistencial Universitario de Salamanca/IBSAL/CIC/Ciberonc, Salamanca, Spain
[10]Dipartimento di Fisica e Astronomia, Università di Bologna, Bologna, Italy
[11]Department of Hematology, Amsterdam UMC, Cancer Center Amsterdam, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[12]University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom
[13]Asklepios Tumorzentrum Hamburg, AK Altona and AK St Georg, Hamburg, Germany
[14]Hospital Clinic, IDIBAPS, Barcelona, Spain
[15]HOVON Data Center, Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands
[16]Department of Hematology, University Clinic Essen, Essen, Germany
[17]The Institute of Cancer Research, London, United Kingdom and The Royal Marsden Hospital, London, United Kingdom
[18]Department of Medicine, University of Salamanca, Institute of Biomedical Research of Salamanca (IBSAL), University of Salamanca—Cancer Research Center of Salamanca (IBMCC, USAL-CSIG). Hematology Department, Hospital Universitario de Salamanca (CAUSA/IBSAL), Salamanca, Spain
[19]Clínica Universidad de Navarra, CIMA, IDISNA, CIBER-ONC (CB16/12/00369), Pamplona, Spain

CORRESPONDING AUTHOR

Mattia D'Agostino, MD, SSD Clinical Trial in Oncoematologia e Mieloma Multiplo, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, via Genova 3, 10126 Torino, Italy; e-mail: mattia.dagostino@unito.it.

PRIOR PRESENTATION

Presented at the American Society of Hematology (ASH) 2019 61st Annual Meeting, Orlando, FL, December 7-10, 2019 (poster) citation: D'Agostino M, Waage A, Lahuerta, J-J, et al: Validation and improvement opportunities of the revised international staging system for multiple myeloma: An analysis on mature data from European clinical trials within the HARMONY big data platform. Blood 134, 2019 (suppl 1; abstr #1773); the American Society of Hematology (ASH) 2020 62nd Meeting, December 5-8, 2020 (poster) citation: D'Agostino M, Lahuerta, J-J, Wester R, et al: A new risk stratification model (R2-ISS) in newly diagnosed multiple myeloma: Analysis of mature data from 7,077 patients collected by European Myeloma Network within HARMONY big data platform. Blood 136:34-37, 2020 (suppl 1; abstr 1329); the European Hematology Association (EHA) 2020 25th Congress, June 11-21, 2020 (poster) citation: D'Agostino M, Lahuerta JJ, Waage A, et al: A new risk stratification strategy in newly diagnosed multiple myeloma: An analysis on mature data from European clinical trials within the HARMONY big data platform. HemaSphere 4:421-422, 2020 (suppl 1; abstr EP933); the European Myeloma Network (EMN) 2021 2nd Meeting, March 3-6, 2021 (poster) citation: D'Agostino M, Lahuerta JJ, Wester R, et al: R2-ISS, a new risk stratification model in newly diagnosed multiple myeloma by the European Myeloma Network within HARMONY big data platform project. HemaSphere 5:24, 2021 (suppl 1; abstr P21); the Italian Society of Hematology/Società Italiana di Ematologia (SIE) 2021 48th Congress, Milan, Italy, October 24-27, 2021 (oral) citation: D'Agostino M, Lahuerta JJ, Wester R, et al: R2-ISS, a new risk stratification model in newly diagnosed multiple myeloma (NDMM): Analysis of 7,077 patient data by the European Myeloma Network (EMN) within HARMONY big data platform project. Haematologica 106:12, 2021 (suppl 3; abstr C007).

SUPPORT

Supported by the IMI-JU funded project HARMONY, Grant Agreement #116026. No professional medical writer was involved in any portion of the preparation of this manuscript.
The analysis of the UK National Cancer Research Institute (NCRI) Myeloma XI trial was supported by Myeloma UK and received infrastructure support by the NIHR Biomedical Research Center at The Institute of Cancer Research and The Royal Marsden Hospital. The UK National Cancer Research Institute (NCRI) Myeloma XI trial was funded by Cancer Research UK (Primary Funder [C1298/A10410; C7852/A25447]).
M.F.K. was supported by a Jacquelin Forbes-Nixon Fellowship.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02614.

DATA SHARING STATEMENT

After the publication of this article, data collected for this analysis and related documents will be made available to others upon reasonably justified request, which needs to be written and addressed to the attention of the corresponding author Dr Mattia D'Agostino at the following e-mail address: mattia.dagostino@unito.it. The HARMONY Alliance, via the corresponding author Dr Mattia D'Agostino, is responsible to evaluate and eventually accept or refuse every request to disclose data and their related documents, in compliance with the ethical approval conditions, in compliance with applicable laws and regulations, and in conformance with the agreements in place with the involved subjects, the participating institutions, and all the other parties directly or indirectly involved in the participation, conduct, development, management, and evaluation of this analysis.

AUTHOR CONTRIBUTIONS

Conception and design: Mattia D'Agostino, Alessandra Larocca, Jesús F. San-Miguel, Mario Boccadoro, Pieter Sonneveld
Financial support: Pieter Sonneveld
Administrative support: Jesús María Hernández Rivas, Pieter Sonneveld
Provision of study materials or patients: Juan José Lahuerta, Elena Zamagni, María-Victoria Mateos, Serena Rocchi, Hans Salwender, Bronno van der Holt, Elias K. Mai, Sonja Zweegman, Martin F. Kaiser, Jesús F. San-Miguel, Pieter Sonneveld
Collection and assembly of data: Mattia D'Agostino, David A. Cairns, Juan José Lahuerta, Ruth Wester, Uta Bertsch, Anders Waage, Niels W. C. J. van de Donk, Graham Jackson, Serena Rocchi, Hans Salwender, Joan Bladé Creixenti, Francesca Bonello, Andrea Capra, Elias K. Mai, Francesca Gay, Michele Cavo, Martin F. Kaiser, Jesús María Hernández Rivas, Alessandra Larocca, Gordon Cook, Mario Boccadoro, Pieter Sonneveld
Data analysis and interpretation: Mattia D'Agostino, David A. Cairns, Elena Zamagni, María-Victoria Mateos, Daniele Dall'Olio, Niels W. C. J. van de Donk, Serena Rocchi, Joan Bladé Creixenti, Bronno van der Holt, Gastone Castellani, Francesca Bonello, Andrea Capra, Elias K. Mai, Francesca Gay, Sonja Zweegman, Hartmut Goldschmidt, Jesús María Hernández Rivas, Alessandra Larocca, Gordon Cook, Mario Boccadoro, Pieter Sonneveld
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors wish to thank all the study participants, referring clinicians, and data managers for their valuable contributions.

HARMONY and HARMONY PLUS are funded through the Innovative Medicines Initiative (IMI), Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients. Funding is received from the IMI 2 Joint Undertaking and is listed under grant agreement for HARMONY No. 116026 and grant agreement for HARMONY PLUS No. 945406. This Joint Undertaking receives support from the European Union's Horizon 2020 Research and Innovation Program and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The communication included in this contribution reflects the authors' view. Neither IMI nor the European Union, EFPIA, or any Associated Partners are responsible for any use that may be made of the information contained therein.

REFERENCES

1. Palumbo A, Anderson K: Multiple myeloma. N Engl J Med 364:1046-1060, 2011
2. Palumbo A, Avet-Loiseau H, Oliva S, et al: Revised international staging system for multiple myeloma: A report from International Myeloma Working Group. J Clin Oncol 33:2863-2869, 2015
3. Caro J, Al Hadidi S, Usmani S, et al: How to treat high-risk myeloma at diagnosis and relapse. Am Soc Clin Oncol Ed Book 41:291-309, 2021
4. Greipp PR, San-Miguel J, Dune BGM, et al: International staging system for multiple myeloma. J Clin Oncol 23:3412-3420, 2005
5. Fonseca R, Bergsagel PL, Drach J, et al: International Myeloma Working Group molecular classification of multiple myeloma: Spotlight review. Leukemia 23: 2210-2221, 2009
6. Dimopoulos MA, Barlogie B, Smith TL, et al: High serum lactate dehydrogenase level as a marker for drug resistance and short survival in multiple myeloma. Ann Intern Med 115:931-935, 1991
7. Terpos E, Katodritou E, Roussou M, et al: High serum lactate dehydrogenase adds prognostic value to the International Myeloma Staging System even in the era of novel agents. Eur J Haematol 85:114-119, 2010
8. Shah V, Sherborne AL, Walker BA, et al: Prediction of outcome in newly diagnosed myeloma: A meta-analysis of the molecular profiles of 1905 trial patients. Leukemia 32:102-110, 2018
9. Caltagirone S, Ruggeri M, Aschero S, et al: Chromosome 1 abnormalities in elderly patients with newly diagnosed multiple myeloma treated with novel therapies. Haematologica 99:1611-1617, 2014
10. Weinhold N, Salwender HJ, Cairns DA, et al: Chromosome 1q21 abnormalities refine outcome prediction in patients with multiple myeloma - A meta-analysis of 2,596 trial patients. Haematologica 106:2754-2758, 2021
11. HARMONY Alliance. https://www.harmony-alliance.eu/
12. Bringhen S, Petrucci MT, Larocca A, et al: Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: A multicenter, phase 2 study. Blood 124:63-69, 2014
13. Magarotto V, Bringhen S, Offidani M, et al: Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma. Blood 127:1102-1108, 2016
14. Bringhen S, D'Agostino M, Paris L, et al: Lenalidomide-based induction and maintenance in elderly newly diagnosed multiple myeloma patients: Updated results of the EMN01 randomized trial. Haematologica 105:1937-1947, 2020
15. Gay F, Oliva S, Petrucci MT, et al: Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: A randomised, multicentre, phase 3 trial. Lancet Oncol 16:1617-1629, 2015
16. Palumbo A, Cavallo F, Gay F, et al: Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med 371:895-905, 2014
17. Palumbo A, Gay F, Falco P, et al: Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients. J Clin Oncol 28:800-807, 2010
18. Gay F, Magarotto V, Crippa C, et al: Bortezomib induction, reduced-intensity transplantation, and lenalidomide consolidation-maintenance for myeloma: Updated results. Blood 122:1376-1383, 2013
19. Palumbo A, Bringhen S, Rossi D, et al: Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: A randomized controlled trial. J Clin Oncol 28:5101-5109, 2010
20. Palumbo A, Bringhen S, Larocca A, et al: Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: Updated follow-up and improved survival. J Clin Oncol 32:634-640, 2014
21. Larocca A, Bringhen S, Petrucci MT, et al: A phase 2 study of three low-dose intensity subcutaneous bortezomib regimens in elderly frail patients with untreated multiple myeloma. Leukemia 30:1320-1326, 2016
22. Sonneveld P, Schmidt-Wolf IGH, van der Holt B, et al: Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: Results of the randomized phase III HOVON-65/GMMG-HD4 trial. J Clin Oncol 30:2946-2955, 2012
23. Goldschmidt H, Lokhorst HM, Mai EK, et al: Bortezomib before and after high-dose therapy in myeloma: Long-term results from the phase III HOVON-65/GMMG-HD4 trial. Leukemia 32:383-390, 2018
24. Cavo M, Tacchetti P, Patriarca F, et al: Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: A randomised phase 3 study. Lancet 376:2075-2085, 2010
25. Tacchetti P, Pantani L, Patriarca F, et al: Bortezomib, thalidomide, and dexamethasone followed by double autologous haematopoietic stem-cell transplantation for newly diagnosed multiple myeloma (GIMEMA-MMY-3006): Long-term follow-up analysis of a randomised phase 3, open-label study. Lancet Haematol 7: e861-e873, 2020
26. Rosiñol L, Oriol A, Teruel AI, et al: Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: A randomized phase 3 PETHEMA/GEM study. Blood 120:1589-1596, 2012
27. Rosiñol Dachs L, Oriol A, Teruel AI, et al: VTD (bortezomib/thalidomide/dexamethasone) as pretransplant induction therapy for multiple myeloma: Definitive results of a randomized phase 3 PETHEMA/GEM study. Blood 132, 2018 (abstr #126)
28. Cavo M, Gay F, Beksac M, et al: Autologous haematopoietic stem-cell transplantation versus bortezomib–melphalan–prednisone, with or without bortezomib–lenalidomide–dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): A multicentre, randomised, open-label, phase 3 study. Lancet Haematol 7:e456-e468, 2020
29. Sonneveld P, Dimopoulos MA, Beksac M, et al: Consolidation and maintenance in newly diagnosed multiple myeloma. J Clin Oncol 39:3613-3622, 2021
30. Mateos M-V, Oriol A, Martínez-López J, et al: Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: A randomised trial. Lancet Oncol 11:934-941, 2010

31. Mateos M-V, Oriol A, Martinez-Lopez J, et al: Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. Blood 120:2581-2588, 2012
32. Mateos M-V, Oriol A, Martinez-Lopez J, et al: GEM2005 trial update comparing VMP/VTP as induction in elderly multiple myeloma patients: Do we still need alkylators? Blood 124:1887-1893, 2014
33. Mateos M-V, Martínez-López J, Hernández M-T, et al: Sequential vs alternating administration of VMP and Rd in elderly patients with newly diagnosed MM. Blood 127:420-425, 2016
34. Zweegman S, van der Holt B, Mellqvist U-H, et al: Melphalan, prednisone, and lenalidomide versus melphalan, prednisone, and thalidomide in untreated multiple myeloma. Blood 127:1109-1116, 2016
35. Mai EK, Bertsch U, Dürig J, et al: Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma. Leukemia 29:1721-1729, 2015
36. Goldschmidt H, Mai EK, Dürig J, et al: Response-adapted lenalidomide maintenance in newly diagnosed myeloma: Results from the phase III GMMG-MM5 trial. Leukemia 34:1853-1865, 2020
37. Jackson GH, Davies FE, Pawlyn C, et al: Response-adapted intensification with cyclophosphamide, bortezomib, and dexamethasone versus no intensification in patients with newly diagnosed multiple myeloma (Myeloma XI): A multicentre, open-label, randomised, phase 3 trial. Lancet Haematol 6:e616-e629, 2019
38. Jackson GH, Davies FE, Pawlyn C, et al: Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 20:57-73, 2019
39. Jackson GH, Pawlyn C, Cairns DA, et al: Optimising the value of immunomodulatory drugs during induction and maintenance in transplant ineligible patients with newly diagnosed multiple myeloma: Results from Myeloma XI, a multicentre, open-label, randomised, Phase III trial. Br J Haematol 192:853-868, 2021
40. Jackson GH, Davies FE, Pawlyn C, et al: Lenalidomide before and after autologous stem cell transplantation for transplant-eligible patients of all ages in the randomized, phase III, Myeloma XI trial. Haematologica 106:1957-1967, 2021
41. Jackson GH, Pawlyn C, Cairns DA, et al: Carfilzomib, lenalidomide, dexamethasone, and cyclophosphamide (KRdc) as induction therapy for transplant-eligible, newly diagnosed multiple myeloma patients (Myeloma XI+): Interim analysis of an open-label randomised controlled trial. PLoS Med 18:e1003454, 2021
42. Butler J, van Speybroeck M, Druml C, et al: D8.03 "Proof-of-Principle" Study: SOP HARMONY Anonymization Procedure. Salamanca, Spain, HARMONY Consortium, 2018. https://cms.harmony-alliance.eu/cgi-bin/itworx/download.cgi?vid=638&uid=-1&dokid=192
43. Belenkaya R, Gurley MJ, Golozar A, et al: Extending the OMOP common data model and standardized vocabularies to support observational cancer research. JCO Clin Cancer Inform 5:12-20, 2021
44. Schmidt TM, Fonseca R, Usmani SZ: Chromosome 1q21 abnormalities in multiple myeloma. Blood Cancer J 11:83, 2021
45. D'Agostino M, Lahuerta J-J, Wester R, et al: A new risk stratification model (R2-ISS) in newly diagnosed multiple myeloma: Analysis of mature data from 7077 patients collected by European Myeloma Network within HARMONY big data platform. Blood 136:34-37, 2020 (abstr 1329)
46. Gerds TA: pec: Prediction Error Curves for Risk Prediction Models in Survival Analysis. R Package Version 2022.03.06, 2022. https://cran.r-project.org/web/packages/pec/
47. Palumbo A, Bringhen S, Mateos M-V, et al: Geriatric assessment predicts survival and toxicities in elderly myeloma patients: An International Myeloma Working Group report. Blood 125:2068-2074, 2015
48. Goldman-Mazur S, Jurczyszyn A, Castillo JJ, et al: A multicenter retrospective study of 223 patients with t(14;16) in multiple myeloma. Am J Hematol 95:503-509, 2020
49. Mina R, Joseph NS, Gay F, et al: Clinical features and survival of multiple myeloma patients harboring t(14;16) in the era of novel agents. Blood Cancer J 10:40, 2020
50. Larocca A, Dold SM, Zweegman S, et al: Patient-centered practice in elderly myeloma patients: An overview and consensus from the European Myeloma Network (EMN). Leukemia 32:1697-1712, 2018
51. Gay F, Musto P, Rota-Scalabrini D, et al: Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): A randomised, open-label, phase 2 trial. Lancet Oncol 22:1705-1720, 2021
52. Facon T, Kumar S, Plesner T, et al: Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med 380:2104-2115, 2019
53. Mateos M-V, Dimopoulos MA, Cavo M, et al: Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med 378:518-528, 2018
54. Voorhees PM, Kaufman JL, Laubach J, et al: Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: The GRIFFIN trial. Blood 136:936-945, 2020
55. Kumar SK, Callander NS, Adekola K, et al: Multiple myeloma, version 3.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 18:1685-1717, 2020
56. Bertamini L, Oliva S, Rota-Scalabrini D, et al: High levels of circulating tumor plasma cells as a key hallmark of aggressive disease in transplant-eligible patients with newly diagnosed multiple myeloma. J Clin Oncol (in press)
57. Garcés J-J, Cedena M-T, Puig N, et al: Circulating tumor cells for the staging of patients with newly diagnosed transplant-eligible multiple myeloma. J Clin Oncol (in press)
58. Walker BA, Mavrommatis K, Wardell CP, et al: A high-risk, double-hit, group of newly diagnosed myeloma identified by genomic analysis. Leukemia 33:159-170, 2019
59. D'Agostino M, Zaccaria GM, Ziccheddu B, et al: Early relapse risk in patients with newly diagnosed multiple myeloma characterized by next-generation sequencing. Clin Cancer Res 26:4832-4841, 2020
60. Perrot A, Lauwers-Cances V, Tournay E, et al: Development and validation of a cytogenetic prognostic index predicting survival in multiple myeloma. J Clin Oncol 37:1657-1665, 2019
61. Barwick BG, Neri P, Bahlis NJ, et al: Multiple myeloma immunoglobulin lambda translocations portend poor prognosis. Nat Commun 10:1911, 2019
62. Montefusco V, Gay F, Spada S, et al: Outcome of paraosseous extra-medullary disease in newly diagnosed multiple myeloma patients treated with new drugs. Haematologica 105:193-200, 2020
63. Usmani SZ, Heuck C, Mitchell A, et al: Extramedullary disease portends poor prognosis in multiple myeloma and is over-represented in high-risk disease even in the era of novel agents. Haematologica 97:1761-1767, 2012
64. Abdallah N, Baughn LB, Vincent Rajkumar S, et al: Implications of MYC rearrangements in newly diagnosed multiple myeloma. Clin Cancer Res 26:6581-6588, 2020
65. Schmidt TM, Barwick BG, Joseph N, et al: Gain of Chromosome 1q is associated with early progression in multiple myeloma patients treated with lenalidomide, bortezomib, and dexamethasone. Blood Cancer J 9:94, 2019

66. D'Agostino M, Belotti A, Zamagni E, et al: Gain and amplification of 1q induce transcriptome deregulation and worsen the outcome of newly diagnosed multiple myeloma patients. Clin Lymphoma Myeloma Leuk 21:S34, 2021 (abstr OAB-055)
67. Kuiper R, Zweegman S, van Duin M, et al: Prognostic and predictive performance of R-ISS with SKY92 in older patients with multiple myeloma: The HOVON-87/NMSG-18 trial. Blood Adv 4:6298-6309, 2020
68. Bertamini L, D'Agostino M, Gay F: MRD assessment in multiple myeloma: Progress and challenges. Curr Hematol Malig Rep 16:162-171, 2021
69. Tandon N, Rajkumar SV, LaPlant B, et al: Clinical utility of the revised international staging system in unselected patients with newly diagnosed and relapsed multiple myeloma. Blood Cancer J 7:e528, 2017

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within the HARMONY Project

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Mattia D'Agostino
Honoraria: Sanofi, GlaxoSmithKline
Consulting or Advisory Role: Sanofi, GlaxoSmithKline

David A. Cairns
Research Funding: Celgene (Inst), Merck Sharp & Dohme (Inst), Amgen (Inst), Takeda (Inst), Sanofi (Inst)
Travel, Accommodations, Expenses: Celgene

Juan José Lahuerta
Consulting or Advisory Role: Celgene, Amgen, Janssen-Cilag, Sanofi
Travel, Accommodations, Expenses: Celgene

Ruth Wester
Honoraria: Sanofi, Janssen

Anders Waage
Honoraria: Janssen Oncology
Speakers' Bureau: Janssen Oncology, Novartis

Elena Zamagni
Honoraria: Janssen-Cilag, Celgene, Amgen, Bristol Myers Squibb, Takeda, GlaxoSmithKline, Oncopeptides, Sanofi
Consulting or Advisory Role: Celgene, Janssen-Cilag, Amgen, Sanofi
Travel, Accommodations, Expenses: Janssen-Cilag, Celgene, Amgen

María-Victoria Mateos
Honoraria: Janssen-Cilag, Celgene, Amgen, Takeda, GlaxoSmithKline, AbbVie/Genentech, Sanofi
Consulting or Advisory Role: Takeda, Janssen-Cilag, Celgene, Amgen, AbbVie, GlaxoSmithKline, Pfizer, Regeneron, Roche/Genentech

Niels W.C.J. van de Donk
Consulting or Advisory Role: Janssen (Inst), Celgene (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Amgen (Inst), Servier (Inst), Takeda (Inst), Bayer (Inst), Adaptive Biotechnologies (Inst)
Speakers' Bureau: Janssen Research & Development, Celgene, Amgen, Bristol Myers Squibb
Research Funding: Janssen (Inst), Celgene (Inst), Amgen (Inst), Novartis (Inst), Bristol Myers Squibb (Inst), Cellectis (Inst)

Graham Jackson
Honoraria: J&J, Sanofi, BMS, Takeda
Consulting or Advisory Role: Oncopeptides, Janssen Oncology, Sanofi, Celgene, Takeda
Research Funding: Takeda

Serena Rocchi
Honoraria: Amgen, Janssen Oncology, GlaxoSmithKline

Hans Salwender
Honoraria: Sebia, Takeda, TAD Pharma, Chugai Pharma
Consulting or Advisory Role: Pfizer, Janssen Oncology, Sanofi, Oncopeptides, GlaxoSmithKline, Amgen, AbbVie, Bristol Myers Squibb/Celgene, Roche, Genzyme

Joan Bladé Creixenti
Honoraria: Janssen, Celgene, Amgen, Takeda, Oncopeptides

Elias K. Mai
Honoraria: Janssen, Takeda, Bristol Myers Squibb/Celgene, Sanofi, GlaxoSmithKline
Consulting or Advisory Role: Janssen, Bristol Myers Squibb/Celgene, Takeda, Sanofi, GlaxoSmithKline
Research Funding: Janssen, Bristol Myers Squibb/Celgene, Takeda, Sanofi, GlaxoSmithKline
Travel, Accommodations, Expenses: Janssen, Bristol Myers Squibb/Celgene, Takeda, GlaxoSmithKline, Sanofi

Jan Dürig
Consulting or Advisory Role: BMS GmbH & Co, KG, Celgene, Janssen, Amgen, Takeda, Roche
Speakers' Bureau: Amgen, BMS GmbH & Co, KG, Janssen
Travel, Accommodations, Expenses: Janssen, BMS GmbH & Co, KG

Francesca Gay
Honoraria: Amgen, Celgene, Janssen, Takeda, Bristol Myers Squibb, AbbVie, GlaxoSmithKline
Consulting or Advisory Role: Amgen, Celgene, Janssen, Takeda, Bristol Myers Squibb, AbbVie, GlaxoSmithKline, Roche, Adaptive Biotechnologies, Oncopeptides, bluebird bio, Pfizer

Sonja Zweegman
Consulting or Advisory Role: Janssen-Cilag (Inst), Takeda (Inst), Celgene (Inst), Sanofi (Inst), Oncopeptides (Inst)
Research Funding: Janssen-Cilag (Inst), Takeda (Inst), Celgene (Inst)
Travel, Accommodations, Expenses: Janssen-Cilag, Takeda, Celgene

Michele Cavo
Honoraria: Janssen, Sanofi, GlaxoSmithKline, Takeda, Amgen, AbbVie, Adaptive Biotechnologies, Celgene/Bristol Myers Squibb, Mundipharma
Speakers' Bureau: Janssen, Celgene/Bristol Myers Squibb

Martin F. Kaiser
Honoraria: Takeda, Celgene, Amgen, Janssen Oncology
Consulting or Advisory Role: Janssen Oncology, Celgene, Bristol Myers Squibb, Takeda, Amgen, AbbVie, GlaxoSmithKline, Seattle Genetics, Pfizer
Research Funding: Celgene (Inst)
Travel, Accommodations, Expenses: Takeda, Janssen, Bristol Myers Squibb/Celgene

Hartmut Goldschmidt
Honoraria: Janssen-Cilag, Novartis, Bristol Myers Squibb, Celgene, Chugai Pharma, Sanofi, Amgen, GlaxoSmithKline
Consulting or Advisory Role: Celgene (Inst), Janssen-Cilag (Inst), Bristol Myers Squibb (Inst), Amgen (Inst), Takeda (Inst), Adaptive Biotechnologies (Inst), Sanofi (Inst)
Research Funding: Bristol Myers Squibb (Inst), Janssen (Inst), Novartis (Inst), Chugai Pharma Europe (Inst), Celgene (Inst), Amgen (Inst), Sanofi (Inst), Mundipharma (Inst), Takeda (Inst), Molecular Partners (Inst), MSD (Inst), Incyte (Inst)
Travel, Accommodations, Expenses: Janssen-Cilag, Sanofi
Other Relationship: Amgen (Inst), Celgene/Bristol Myers Squibb (Inst), Chugai Pharma Europe (Inst), Janssen (Inst), Sanofi (Inst)

Jesús María Hernández Rivas
Honoraria: GlaxoSmithKline, Pfizer
Consulting or Advisory Role: Amgen, Bristol Myers Squibb/Celgene
Speakers' Bureau: Amgen
Research Funding: Pfizer (Inst)
Travel, Accommodations, Expenses: Novartis

Alessandra Larocca
Honoraria: Janssen-Cilag, Bristol Myers Squibb, Amgen, Takeda, Oncopeptides, GlaxoSmithKline, Sanofi, Karyopharm Therapeutics
Consulting or Advisory Role: Janssen-Cilag, Bristol Myers Squibb, Amgen, Takeda, Oncopeptides, GlaxoSmithKline, Sanofi, Karyopharm Therapeutics

Gordon Cook
Honoraria: Takeda, Janssen-Cilag, Celgene, Karyopharm Therapeutics, Bristol Myers Squibb, Amgen, Oncopeptides
Consulting or Advisory Role: Janssen, Bristol Myers Squibb, Amgen, Takeda, Karyopharm Therapeutics, Oncopeptides
Speakers' Bureau: Takeda, Janssen-Cilag, Amgen, Jazz Pharmaceuticals, Takeda
Research Funding: Takeda (Inst), Celgene (Inst)
Travel, Accommodations, Expenses: Takeda

Jesús F. San-Miguel
Consulting or Advisory Role: Amgen (Inst), Celgene (Inst), Takeda (Inst), Bristol Myers Squibb (Inst), MSD (Inst), Novartis (Inst), Sanofi (Inst), Janssen (Inst), Roche (Inst), AbbVie (Inst), GlaxoSmithKline (Inst), Karyopharm Therapeutics (Inst), Secura Bio (Inst), Regeneron (Inst), Haemalogix (Inst)

Mario Boccadoro
Honoraria: Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol Myers Squibb, AbbVie
Consulting or Advisory Role: Janssen, GlaxoSmithKline
Research Funding: Sanofi (Inst), Celgene (Inst), Amgen (Inst), Janssen (Inst), Novartis (Inst), Bristol Myers Squibb (Inst), Mundipharma (Inst)

Pieter Sonneveld
Consulting or Advisory Role: Celgene, Janssen, Amgen, Karyopharm Therapeutics, CARsgen Therapeutics
Research Funding: Janssen (Inst), Amgen (Inst), Skyline Diagnostics (Inst), BMS (Inst)

No other potential conflicts of interest were reported.

Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within the HARMONY Project

Data Supplement

Supplementary methods and results

HARMONY data quality gate

The minimal essential data to be registered in the HARMONY Big Data Platform were unique patient record identifier, diagnosis date, year of birth, protocol code, randomization arm, gender, transplant eligibility, death occurrence, treatment discontinuation, date of the last follow-up, time-to-progression (TTP) event, TTP date, TTP in months, progression-free survival (PFS) event, PFS date, PFS in months, overall survival (OS) event, OS date, and OS in months.
Patients who had incomplete data about the above-mentioned variables were not included in the HARMONY Big Data Platform and, consequently, were not included in this analysis.

Features included in the analyses

The stages of the International Staging System (ISS I, II, III) were defined as described in the main manuscript (see the *Patients* section), according to serum β2-microglobulin and albumin levels.[1]
Serum levels of lactate dehydrogenase (LDH) were measured at baseline. The upper limit of normal (ULN) ranges were defined by the local laboratories. High LDH was defined as >ULN; Normal LDH as ≤ULN.
The stages of the Revised ISS (R-ISS I, II, III) were defined as previously described, according to ISS stage, high-risk CA [defined as the presence of at least one among del(17p) deletion, t(4;14)(p16;q32) translocation, and/or t(14;16)(q32;q23) translocation], and LDH levels.[2]
The Eastern Cooperative Oncology Group performance status (ECOG PS) was assessed by the treating physician at the diagnosis of multiple myeloma (MM).
The heavy chain isotype of myeloma-specific monoclonal protein was evaluated at baseline through immune fixation.
Creatinine clearance was calculated according to the Modification of Diet in Renal Disease (MDRD) formula.[3]
The following risk factors were compared: ISS stage (II vs. I, III vs. I, not available [NA] vs. I); LDH (>upper limit of normal [ULN] vs. ≤ULN, NA vs. ≤ULN); del(17p) (Yes vs. No, NA vs. No); t(4;14) (Yes vs. No, NA vs. No); 1q gain/amplification ([1q+], Yes vs. No, NA vs. No); t(14;16) (Yes vs. No, NA vs. No); Eastern Cooperative Oncology Group performance status ([ECOG PS], >1 vs. ≤1, NA vs. ≤1);[4] heavy chain isotype (IgA vs. non-IgA, NA vs. non-IgA);[5] and creatinine clearance (≤45 vs. >45 ml/min, NA vs. >45 ml/min).[6]

Chromosomal abnormalities

Analyses were performed by interphase fluorescence in situ hybridization (FISH) in few European laboratories. Despite the inter-laboratory variability, all analyses were performed on purified plasma cells obtained with immunomagnetic techniques, and the analyses of del(17p), t(4;14), 1q+, and t(14;16) were commonly included in each multiple myeloma (MM) panel and tested using commercial probes. Of note, although the cut-off levels were not identical, they were very similar, ranging from 10% to 20% for numerical aberrations and from 10% to 15% for IgH translocations.
Translocations and copy-number alterations in the United Kingdom National Cancer Research Institute (UK NCRI) Myeloma XI trial were centrally analyzed by real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR) and multiplex ligation-dependent probe amplification (MLPA, a technique validated against FISH), as previously described.[7]

Grouping strategy

In the Second Revision of the International Staging System (R2-ISS) score, in order to identify 4 risk-defined groups, we defined the cut-offs according to the highest possible C-index

estimate by using the inverse probability of censoring weighted (IPCW) method with the following constraints: 1) each group must be represented by at least 5% of the total population and (2) the 5-year survival probability of the highest-risk group must be less than 40% (representing the 5-year survival probability of R-ISS III patients).[2] The cut-offs with the best performances are shown in *Table S3*, while the final grouping strategy is shown in *Table 2* and *Figure S2*.

Proportional hazards assessment

A log-negative log plot by R2-ISS risk group for OS was performed in the training (*Figure S3a*) and validation (*Figure S3b*) sets as a visual approach to evaluate the proportional hazards assumption.

OS calibration of the R2-ISS

In order to test the OS calibration of the R2-ISS, we focused on transplant-eligible patients receiving a treatment based on an immunomodulatory drug (IMiD). This population was well represented and similarly treated both in the training (n=234) and validation (n=547) sets.
Of note, patients belonging to the same R2-ISS risk group did not show significant differences in the training vs. validation sets, and the median OS and 5-year OS rates were very similar (*Figure S5*).

Inverse probability of censoring weighted (IPCW) method to estimate the C-index for OS according to the R2-ISS and R-ISS

In order to test the OS discrimination in the training and validation cohorts of the R2-ISS and to compare it with that of the R-ISS, we computed the C-index estimates at different time points according to the IPCW method (*Table S4*). We used the IPCW method in order to avoid bias due to the underlying censoring distribution. A Cox censoring model was used for the IPCW method. Ties in the discrete predictors were removed in order to avoid bias due to a comparison between a four-category classifier (R2-ISS) and a three-category classifier (R-ISS).
The R2-ISS showed similar C-index estimates in the training and validation cohorts.
The R2-ISS and R-ISS showed similar C-index estimates (slightly higher C-index estimates for the R-ISS in the training set and slightly higher C-index estimates for the R2-ISS in the validation set). In conclusion, the R2-ISS was able to discriminate OS in both cohorts, and its main advantage over the R-ISS was not a clear C-index estimate advantage, but a better distribution of patients with intermediate-risk newly diagnosed MM.

Supplementary tables

Table S1. Patient demographics in the sixteen studies included in the analysis

		All N=10843 (%)	*EMN01* n=654 (%)	*EMN02/HO95 MM* n=1493 (%)	*GEM05MAS65* n=259 (%)	*GEM05MENOS65* n=389 (%)	*GEM2010MAS65* n=236 (%)	*GIMEMA-MM-03-05* n=511 (%)	*HOVON-65/ GMMG-HD4* n=826 (%)	*HOVON-87/ NMSG-18* n=630 (%)	*IST-CAR-506* n=58 (%)	*MM-BO2005* n=474 (%)	*GMMG-MM5* n=502 (%)	*26866138 MMY2069* n=152 (%)	*RV-MM-EMN-441* n=387 (%)	*RV-MM-PI-114* n=102 (%)	*RV-MM-PI-209* n=399 (%)	*UK NCRI Myeloma XI** n=3771 (%)
Gender	**F**	4783 (44)	335 (51)	630 (42)	124 (48)	212 (54)	112 (47)	259 (51)	327 (40)	288 (46)	31 (53)	201 (42)	202 (40)	74 (49)	192 (50)	49 (48)	180 (45)	1567 (42)
	M	6060 (56)	319 (49)	863 (58)	135 (52)	177 (46)	124 (53)	252 (49)	499 (60)	342 (54)	27 (47)	273 (58)	300 (60)	78 (51)	195 (50)	53 (52)	219 (55)	2204 (58)
ISS	**I**	3356 (32)	181 (28)	579 (39)	63 (24)	150 (39)	53 (23)	115 (28)	287 (38)	159 (26)	16 (28)	215 (45)	193 (38)	41 (27)	170 (44)	48 (53)	191 (48)	895 (26)
	II	4196 (41)	296 (45)	584 (39)	109 (42)	159 (41)	106 (46)	187 (46)	280 (37)	301 (48)	19 (33)	182 (38)	162 (32)	44 (29)	151 (39)	30 (33)	114 (29)	1472 (42)
	III	2807 (27)	177 (27)	330 (22)	87 (34)	80 (21)	73 (31)	105 (26)	188 (25)	163 (26)	23 (40)	77 (16)	147 (29)	67 (44)	66 (17)	12 (13)	94 (24)	1118 (32)
	Missing	484	0	0	0	0	4	104	71	7	0	0	0	0	0	12	0	286
LDH	**≤ULN**	7574 (81)	473 (89)	1183 (85)	230 (89)	327 (84)	205 (89)	373 (88)	652 (82)	479 (90)	35 (88)	385 (90)	384 (77)	82 (83)	310 (93)	78 (91)	361 (90)	2017 (68)
	>ULN	1810 (19)	56 (11)	210 (15)	29 (11)	62 (16)	25 (11)	51 (12)	142 (18)	51 (10)	5 (12)	43 (10)	116 (23)	17 (17)	24 (7)	8 (9)	38 (10)	933 (32)
	Missing	1459	125	100	0	0	6	87	32	100	18	46	2	53	53	16	0	821
del(17p)	**No**	6414 (89)	460 (86)	1102 (89)	207 (90)	307 (94)	155 (91)	321 (85)	536 (89)	389 (90)	43 (84)	409 (93)	412 (89)	109 (85)	236 (89)	66 (85)	238 (85)	1424 (91)
	Yes	768 (11)	76 (14)	140 (11)	24 (10)	19 (6)	15 (9)	55 (15)	65 (11)	43 (10)	8 (16)	33 (7)	53 (11)	19 (15)	29 (11)	12 (15)	42 (15)	135 (9)
	Missing	3661	118	251	28	63	66	135	225	198	7	32	37	24	122	24	119	2212
t(4;14)	**No**	6131 (87)	471 (89)	1055 (88)	210 (91)	288 (87)	93 (81)	317 (84)	441 (86)	423 (91)	42 (82)	354 (80)	412 (89)	119 (93)	215 (84)	63 (80)	247 (85)	1381 (89)
	Yes	887 (13)	59 (11)	143 (12)	20 (9)	43 (13)	22 (19)	59 (16)	70 (14)	40 (9)	9 (18)	87 (20)	49 (11)	9 (7)	41 (16)	16 (20)	42 (15)	178 (11)
	Missing	3825	124	295	29	58	121	135	315	167	7	33	41	24	131	23	110	2212
1q+	**No**	2801 (65)	9 (56)	731 (62)	0	0	0	73 (55)	430 (73)	223 (63)	0	0	269 (60)	0	9 (56)	9 (45)	14 (78)	1034 (66)
	Yes	1528 (35)	7 (44)	440 (38)	0	0	0	59 (45)	163 (27)	131 (37)	0	0	181 (40)	0	7 (44)	11 (55)	4 (22)	525 (34)
	Missing	6514	638	322	259	389	236	379	233	276	58	474	52	152	371	82	381	2212
Treatment	**IMiDs**	6183 (57)	654 (100)			103 (26)			414 (50)	630 (100)		238 (50)			387 (100)		399 (100)	3358 (89)
	IMiDs plus PIs	3634 (34)		1493 (100)	176 (68)	222 (57)	236 (100)	254 (50)				236 (50)	502 (100)			102 (100)		413 (11)
	PIs	1026 (9)			83 (32)	64 (16)		257 (50)	412 (50)		58 (100)			152 (100)				

		All N=10843 (%)	*EMN01* n=654 (%)	*EMN02/HO95 MM* n=1493 (%)	*GEM05MAS65* n=259 (%)	*GEM05MENOS65* n=389 (%)	*GEM2010MAS65* n=236 (%)	*GIMEMA-MM-03-05* n=511 (%)	*HOVON-65/GMMG-HD4* n=826 (%)	*HOVON-87/NMSG-18* n=630 (%)	*IST-CAR-506* n=58 (%)	*MM-BO2005* n=474 (%)	*GMMG-MM5* n=502 (%)	*26866138 MMY2069* n=152 (%)	*RV-MM-EMN-441* n=387 (%)	*RV-MM-PI-114* n=102 (%)	*RV-MM-PI-209* n=399 (%)	*UK NCRI Myeloma XI** n=3771 (%)
ASCT eligibility	**NTE**	4281 (39)	654 (100)		259 (100)		236 (100)	511 (100)		630 (100)	58 (100)			152 (100)				1781 (47)
	TE	6562 (61)		1493 (100)		389 (100)			826 (100)			474 (100)	502 (100)		387 (100)	102 (100)	399 (100)	1990 (53)
Evaluable to calculate R2-ISS	**No**	7403 (68)	643 (98)	524 (35)	259 (100)	389 (100)	236 (100)	412 (81)	431 (52)	369 (59)	58 (100)	474 (100)	60 (12)	152 (100)	372 (96)	86 (84)	381 (95)	2557 (68)
	Yes	3440 (32)	11 (2)	969 (65)				99 (19)	395 (48)	261 (41)			442 (88)		15 (4)	16 (16)	18 (5)	1214 (32)
R2-ISS	**I**	563 (16)	1 (9)	197 (20)				13 (13)	82 (21)	42 (16)			82 (19)		4 (27)	2 (12)	5 (28)	135 (11)
	II	1008 (29)	2 (18)	302 (31)				24 (24)	122 (31)	97 (37)			119 (27)		7 (47)	5 (31)	8 (44)	322 (27)
	III	1544 (45)	7 (64)	392 (40)				52 (53)	149 (38)	105 (40)			195 (44)		4 (27)	8 (50)	5 (28)	627 (52)
	IV	325 (9)	1 (9)	78 (8)				10 (10)	42 (11)	17 (7)			46 (10)		0 (0)	1 (6)	0 (0)	130 (11)
	Missing	7403	643	524	259	389	236	412	431	369	58	474	60	152	372	86	381	2557

Patients not passing the HARMONY data quality gate were excluded from the analysis.

**518 patients receiving KCRd (carfilzomib, cyclophosphamide, lenalidomide, and dexamethasone) were not included because overall survival data were not available in the HARMONY Big Data Platform.*

Abbreviations. F, female; M, male; ISS, International Staging System stage, LDH, lactate dehydrogenase; ULN, upper limit of normal; del, deletion; t, translocation; 1q+, 1q gain/amplification; IMiDs, immunomodulatory drugs; PIs, proteasome inhibitors; ASCT, autologous stem-cell transplantation; TE, transplant-eligible patients; NTE, non-transplant-eligible patients; R2-ISS, Second Revision of the ISS stage; UK NCRI, United Kingdom National Cancer Research Institute.

Table S2. Treatment regimens in the source studies

Trial	Regimens and doses	No. of randomized patients	Age, median, years (IQR)
EMN01[8,9] ClinicalTrials.gov ID NCT01093196	ARM A R: lenalidomide os 25 mg/die for 21 days D: dexamethasone os 40 mg d 1, 8, 15, 22 or 20 mg in patients aged >75 years	217	73 (70-77)
	ARM B M: melphalan os 0.18 mg/Kg or 0.13 mg/Kg in patients aged >75 years d 1–4 P: prednisone os 1.5 mg/Kg d1–4 R: lenalidomide os 10 mg/die for 21 days	217	
	ARM C C: cyclophosphamide os 50 mg/die for 21 days or 50 mg every other day in patients aged >75 years P: prednisone os 25 mg every other day R: lenalidomide os 25 mg/d for 21 days (nine 28-day cycles followed by maintenance treatment with lenalidomide or lenalidomide and prednisone)	220	
EMN02/HO95[10,11] **(HOVON 95 MM)** ClinicalTrials.gov ID NCT01208766	4 bortezomib-cyclophosphamide-dexamethasone induction cycles ARM A V: bortezomib iv (sc after protocol amendment) 1.3 mg/mq d 1, 4, 8, 11, 22, 25, 29, 32 M: melphalan os 9mg/m^2 d 1–4 P: prednisone os 60 mg/m^2 d 1–4 (four 6-week cycles followed by bortezomib-lenalidomide-dexamethasone consolidation and lenalidomide maintenance or no consolidation and lenalidomide maintenance)	495	58 (52-62)
	ARM B 1 or 2 cycles of melphalan iv 200 mg/m^2 followed by stem-cell support (followed by bortezomib-lenalidomide-dexamethasone consolidation and lenalidomide maintenance or no consolidation and lenalidomide maintenance)	702	

GEM05MAS65[12–14] ClinicalTrials.gov ID NCT00443235	ARM A V: bortezomib iv 1.3 mg/m^2 d 1, 4, 8, 11, 22, 25, 29, 32 of cycle 1 followed by iv bortezomib (1.3 mg/m^2) d 1, 8, 15, 22 M: melphalan os 9mg/m^2 d 1–4 P: prednisone os 60 mg/m^2 d 1–4 (one 6-week cycle and five 5-week cycles followed by maintenance treatment with bortezomib-thalidomide or bortezomib-prednisone) ARM B V: bortezomib iv 1.3 mg/m^2 d 1, 4, 8, 11, 22, 25, 29, 32 of cycle 1 followed by iv bortezomib (1.3 mg/m^2) d 1, 8, 15, 22 T: thalidomide os 100 mg daily P: prednisone os 60 mg/m^2 d 1–4 (one 6-week cycle and five 5-week cycles followed by maintenance treatment with bortezomib-thalidomide or bortezomib-prednisone)	130 130	73 (69-76)
GEM05MENOS65[15,16] ClinicalTrials.gov ID NCT00461747	ARM A V: vincristine iv 0.03 mg/kg (upper limit, 2 mg) d 1 B: BCNU 0.5 mg/kg iv d 1 M: melphalan 0.25 mg/kg os d 1–4 C: cyclophosphamide 10 mg/Kg iv d 1 P: prednisone 1 mg/kg d 1–4, 0.5 mg/kg d 5–8, and 0.25 mg/kg d 9–12 V: vincristine 1 mg iv d 1 B: BCNU 30 mg/m^2 iv d 1 A: doxorubicin 40 mg/m^2 iv d 1 D: dexamethasone 40 mg per os d 1–4, 9–12, 17–20. (four 35-day alternating cycles, followed by two bortezomib cycles d 1, 4, 8, 11, followed by 1 or 2 cycles of melphalan 200 mg/m^2 and stem-cell support) ARM B T: thalidomide os 200 mg daily (with escalating doses from 50 mg to 100 mg to 200 mg) D: dexamethasone os 40 mg d 1–4, and 9–12 (six 4-week cycles, followed by 1 or 2 cycles of melphalan 200 mg/m^2 and stem-cell support) ARM C V: bortezomib iv 1.3 mg/m^2 d 1, 4, 8, 11 T: thalidomide os 200 mg daily (with escalating doses from 50 mg to 100 mg to 200 mg) D: dexamethasone os 40 mg d 1–4, 9–12 (six 4-week cycles, followed by 1 or 2 cycles of melphalan 200 mg/m^2 and stem-cell support)	129 127 130	57 (51-61)

GEM2010MAS65[17] ClinicalTrials.gov ID NCT01237249	ARM A (sequential) V: bortezomib iv 1.3 mg/m^2 d 1, 4, 8, 11, 22, 25, 29, 32 of cycle 1, followed by iv bortezomib (1.3 mg/m^2) d 1, 8, 15, 22 M: melphalan os 9 mg/m^2 d 1–4 P: prednisone os 60 mg/m^2 d 1–4 (one 6-week cycle and eight 4-week cycles) R: lenalidomide 25 d 1–21 d: Dexamethasone 40 mg d 1, 8, 15, 22 (nine 4-week cycles) ARM B (alternating) V: bortezomib iv 1.3 mg/m^2 d 1, 4, 8, 11, 22, 25, 29, 32 of cycle 1 followed by iv bortezomib (1.3 mg/m^2) d 1, 8, 15, 22 M: melphalan os 9mg/m^2 d 1–4 P: prednisone os 60 mg/m^2 d 1–4 (one 6-week cycle and eight 4-week cycles) R: lenalidomide 25 d 1–21 d: Dexamethasone 40 mg d 1, 8, 15, 22 (nine 4-week cycles)	118 115	74 (70-78)
GIMEMA-MM-03-05[18,19] ClinicalTrials.gov ID NCT01063179	ARM A V: bortezomib iv 1.3 mg d 1, 8, 15, 22 M: melphalan os 9 mg/m^2 d 1–4 or 2 mg every other day P: prednisone os 60 mg/m^2 d 1–4 ARM B V: bortezomib iv 1.3 mg/m^2 d 1, 8, 15, 22 M: melphalan os 9 mg/m^2 d 1–4 P: prednisone os 60 mg/m^2 d 1–4 T: thalidomide os 50 mg (only in the VMPT arm: nine 28-day cycles followed by maintenance treatment with bortezomib and thalidomide until PD)	257 254	71 (69-75.5)

HOVON-65/GMMG-HD4[20,21] EudraCT No. 2004-000944-26	ARM A V: vincristine iv 0.4 mg d 1–4 A: doxorubicin iv 9 mg/m^2 d 1–4 D: dexamethasone os 50 mg d 1–4, 9–12, 17–20 (three 28-day cycles, followed by 1 or 2 cycles of melphalan 200 mg/m^2 and stem-cell support, followed by maintenance treatment with thalidomide 50 mg per day for 2 years) ARM B P: bortezomib iv 1.3 mg d 1, 4, 8, 11 A: doxorubicin iv 9 mg/m^2 d 1–4 D: dexamethasone os 50 mg d 1–4, 9–12, 17–20 (three 28-day cycles, followed by 1 or 2 cycles of melphalan 200 mg/m^2 and stem-cell support, followed by maintenance treatment with iv bortezomib 1.3 mg/m^2 once every 2 weeks for 2 years)	414 412	57 (51-61)
HOVON-87/NMSG-18[22] EudraCT No. 2007-004007-34	ARM A M: melphalan os 0.18 mg/Kg d 1–4 P: prednisone os 2 mg/Kg d 1–4 T: thalidomide 200 m daily (nine 4-week cycles followed by thalidomide maintenance) ARM B M: melphalan os 0.18mg/Kg d 1–4 P: prednisone os 2 mg/Kg d 1–4 R: lenalidomide 25 mg d 1–21 (nine 4-week cycles followed by lenalidomide maintenance)	318 319	73 (70-77.8)
IST-CAR-506[23] ClinicalTrials.gov ID NCT01346787	C: carfilzomib iv 20 mg/m^2 d 1, 2 of cycle 1, followed by 36 mg/m^2 d 8, 9, 15, 16 of all subsequent cycles C: cyclophosphamide os 300 mg/m^2 d 1, 8, 15 D: dexamethasone os 40 mg d 1, 8, 15, 22 (nine 28-day cycles followed by maintenance treatment with carfilzomib alone until PD)	58	71 (68-75.8)

MM-BO2005[24,25] ClinicalTrials.gov ID NCT01134484	ARM A V: bortezomib iv 1.3 mg d 1, 4, 8, 11 T: thalidomide os 100 mg daily for the first 14 days and 200 mg daily thereafter D: dexamethasone os 40 mg d 1, 2, 4, 5, 8, 9, 11, 12 (three 21-day cycles, followed by 2 cycles of melphalan iv 200 mg/m^2 and stem-cell support, followed by consolidation with 2 VTD cycles) ARM B T: thalidomide os 100 mg daily for the first 14 days and 200 mg daily thereafter D: dexamethasone os 40 mg d 1, 2, 4, 5, 8, 9, 11, 12 (three 21-day cycles, followed by 2 cycles of melphalan 200 mg/m^2 and stem-cell support, followed by consolidation with 2 TD cycles)	236 238	57 (52-62)
GMMG-MM5[26,27] EudraCT No. 2010-019173-16	ARM A1 + B1 P: bortezomib 1.3 mg/m^2 d 1, 4, 8, 11 A: doxorubicin iv 9 mg/m^2 d 1–4 D: dexamethasone os 20 mg d 1–4, 9–12, 17–20 (three 4-week cycles followed by single MEL200-ASCT or tandem MEL200-ASCT in patients with a response less than near CR, followed by lenalidomide consolidation and lenalidomide maintenance until progression or for 2 years [arms A1+A2] or until achievement of CR [arms B1+B2]) ARM A2 + B2 V: bortezomib 1.3 mg/m^2 d 1, 4, 8, 11 C: cyclophosphamide 900 mg/m^2 iv d 1 D: dexamethasone os 40 mg d 1–2, 4–5, 8–9, 11–12 (three 3-week cycles followed by single MEL200-ASCT or tandem MEL200-ASCT in patients with a response less than near CR, followed by lenalidomide consolidation and lenalidomide maintenance until progression or for 2 years [arms A1+A2] or until achievement of CR [arms B1+B2])	251 251	59 (52.3-64)

26866138MMY2069[28] ClinicalTrials.gov ID NCT01190787	GROUP 1 V: bortezomib sc 1.3 mg/m^2 d 1, 8, 15, 22 P: prednisone os 50 mg every other day GROUP 2 C: cyclophosphamide os 50 mg every other day V: bortezomib sc 1.3 mg/m^2 d 1, 8, 15, 22 P: prednisone os 50 mg every other day GROUP 3 V: bortezomib sc 1.3 mg d 1, 8, 15, 22 M: melphalan os 2 mg every other day P: prednisone os 50 mg every other day (nine 28-day cycles followed by maintenance treatment with bortezomib until PD)	51 51 50	77 (74.8-80)
RV-MM-EMN-441[29] ClinicalTrials.gov ID NCT01091831	4 lenalidomide-dexamethasone induction cycles ARM A C: cyclophosphamide os 300 mg/m^2 d 1, 8, 15 R: lenalidomide os 25 mg/d for 21 days D: dexamethasone os 40 mg d 1, 8, 15, 22 (six 28-day cycles followed by maintenance treatment with lenalidomide or lenalidomide and prednisone) ARM B 2 cycles of melphalan iv 200 mg/m^2 followed by stem-cell support (followed by maintenance treatment with lenalidomide or lenalidomide and prednisone)	129 127	57 (53-62)
RV-MM-PI-114[30,31] EudraCT No. 2005-004730-41	P: bortezomib iv 1.3 mg, d 1, 4, 8, 11 A: pegylated liposomal doxorubicin iv 30 mg/m^2 d 4 D: dexamethasone d 1–4, 8–11, 15–18 of cycle 1 and d 1–4 of cycles 2 to 4 2 cycles of melphalan iv 100 mg/m^2 followed by consolidation with lenalidomide 25 mg/d for 21 days + prednisone 50 mg every other day followed by maintenance treatment with lenalidomide 10 mg/d for 21 days until PD	102	67 (63-70)

MM-RV-PI-209[32] ClinicalTrials.gov ID NCT00551928	4 lenalidomide-dexamethasone induction cycles ARM A M: melphalan os 0.18 mg/Kg d 1–4 P: prednisone os 2 mg/Kg d 1–4 R: lenalidomide os 10 mg/d for 21 days (six 28-day cycles followed by maintenance treatment with lenalidomide or no maintenance) ARM B 2 cycles of melphalan iv 200 mg/m^2 followed by stem-cell support (followed by maintenance treatment with lenalidomide or no maintenance)	132 141	58 (52-61)
UK NCRI Myeloma XI[33–37] ISRCTN Registry No. ISRCTN49407852 EudraCT No. 2009-010956-93 ClinicalTrials.gov ID NCT01554852 Primary Funder Cancer Research UK [C1298/A10410] [C7852/A25447]	INTENSIVE TREATMENT PATHWAY CTD: 21-day cycles of cyclophosphamide (C) 500 mg os d 1, 8, 15; thalidomide (T) 100 mg (increasing to 200 mg as tolerated) os daily; and dexamethasone (D) 40 mg os d 1–4, 12–15 CRD: 28-day cycles of cyclophosphamide (C) 500 mg os d 1, 8; lenalidomide (R) 25 mg os d 1–21; and dexamethasone (D) 40 mg os d 1–4, 12–15 KCRD: 28-day cycles of carfilzomib (K) 36mg/m^2 iv d 1–2, 8–9, 15–16; cyclophosphamide (C) 500mg os d 1, 8, lenalidomide (R) 25mg os d 1-21; and dexamethasone (D) 40mg os d 1–4, 8–9, 15–16 Initial induction treatment was administered in the absence of toxicity, consent withdrawal, or progression, for a minimum of 4 cycles and until maximum response followed by high-dose melphalan + ASCT. NON-INTENSIVE TREATMENT PATHWAY aCTD: 28-day attenuated cycles of cyclophosphamide (C) 500 mg os d 1, 8, 15, 22; thalidomide (T) 50 mg (increasing to 200 mg as tolerated) os daily; and dexamethasone (D) 20 mg os d 1–4, 15–18 aCRD: 28-day attenuated cycles of cyclophosphamide (C) 500 mg os d 1, 8; lenalidomide (R) 25 mg os d 1–21; and dexamethasone (D) 20 mg os d 1–4, 15–18. BOTH TREATMENT PATHWAYS Suboptimal responders (<VGPR) not receiving KCRD received intensification with bortezomib plus dexamethasone and cyclophosphamide (VCD). Eligible patients who completed induction therapy according to the protocol received maintenance treatment with lenalidomide or no maintenance.	2568 1852	68 (60-74)

Abbreviations. No., number; IQR, interquartile range; PD, progressive disease; os, oral administration; iv, intravenous administration; sc, subcutaneous administration; d, day; MEL200, melphalan at 200 mg/m^2; ASCT, autologous stem-cell transplantation; CR, complete response; a-, attenuated; VGPR, very good partial response; ID, identifier; UK NCRI, United Kingdom National Cancer Research Institute.

Table S3. Performances of the possible cut-offs according to different grouping strategies

The cut-offs with the highest C-index were selected for grouping.

Group cut-offs	C-index estimate at 60 months	Smallest group proportion, % of the total training set	5-year OS of the high-risk group, %
0 / 0.5-1 / 1.5-2.5 / 3-5	**0.7227**	**8.76%**	**36.95%**
0 / 0.5-1.5 / 2-2.5 / 3-5	0.7214	8.76%	36.95%
0-0.5 / 1 / 1.5-2.5 / 3-5	0.7146	8.76%	36.95%
0-0.5 / 1-1.5 / 2-2.5 / 3-5	0.7095	8.76%	36.95%
0-1 / 1.5 / 2-2.5 / 3-5	0.7083	8.76%	36.95%

Abbreviations. OS, overall survival.

Table S4. IPCW method to estimate the C-index according to the R2-ISS and R-ISS

Patient population	Risk score	C-index estimate at 60 months	C-index estimate at 90 months	C-index estimate at 120 months
Training set	R2-ISS	72.3	70.6	70
Training set	R-ISS	73.1	71.5	70.6
Validation set	R2-ISS	71.2	69.6	NA
Validation set	R-ISS	68.2	68.0	NA

Abbreviations. IPCW, inverse probability of censoring weighted; R2-ISS, Second Revision of the International Staging System; R-ISS, Revised International Staging System; NA, not available.

Table S5. R-ISS distribution according to the R2-ISS in evaluable patients included in the training set (n=2226)

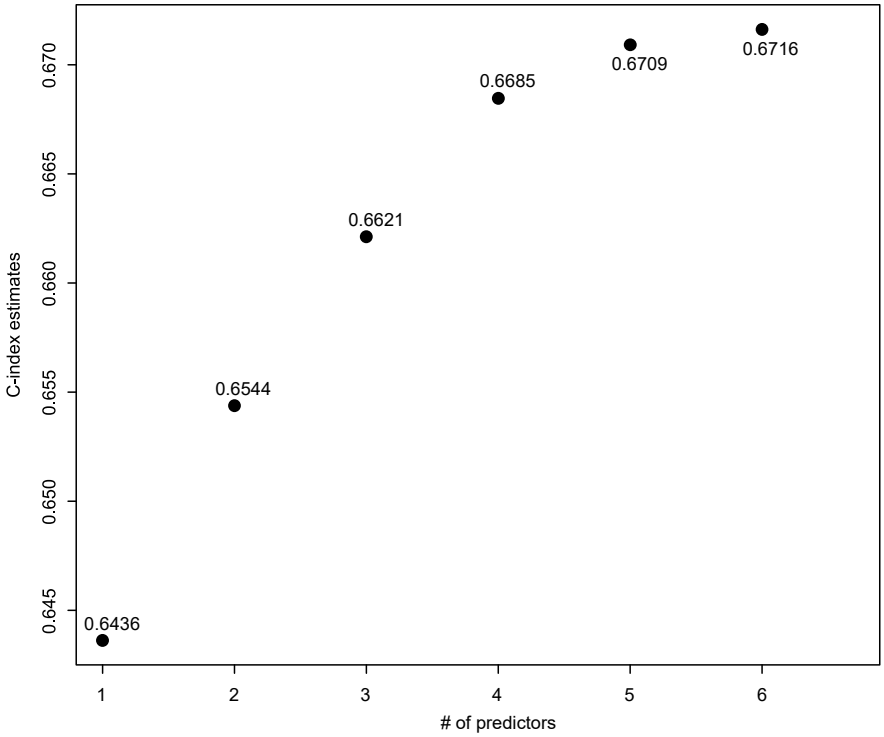
Prognostic score	R2-ISS low (I, n=428)	R2-ISS low-int (II, n=686)	R2-ISS int-high (III, n=917)	R2-ISS high (IV, n=195)
R-ISS I	428	169	0	0
R-ISS II	0	517	811	44
R-ISS III	0	0	106	151

Abbreviations. R-ISS, Revised International Staging System; R2-ISS, Second Revision of the International Staging System; int, intermediate.

Supplementary figures

Figure S1. C-index estimates according to the number of features included in the R2-ISS score calculation

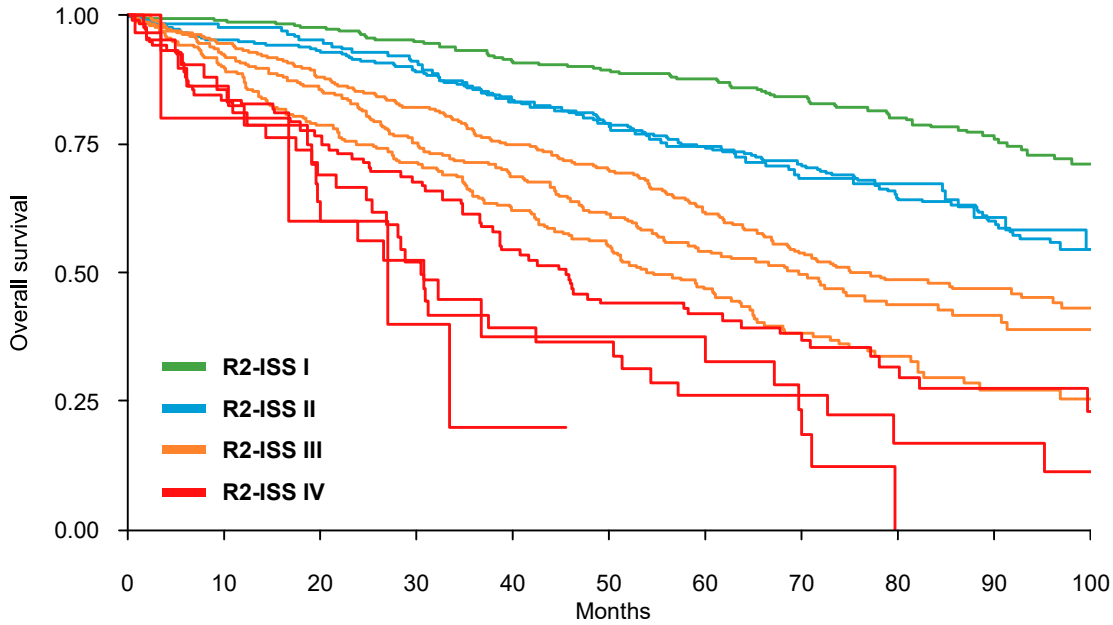
C-index estimates defined using the inverse probability of censoring weighted (IPCW) method at 60 months are shown.



Abbreviations. R2-ISS, Second Revision of the International Staging System.

Figure S2. OS according to the continuous score calculation

Each curve represents a 0.5 score point. Curves of the same color were grouped together in the final R2-ISS model.

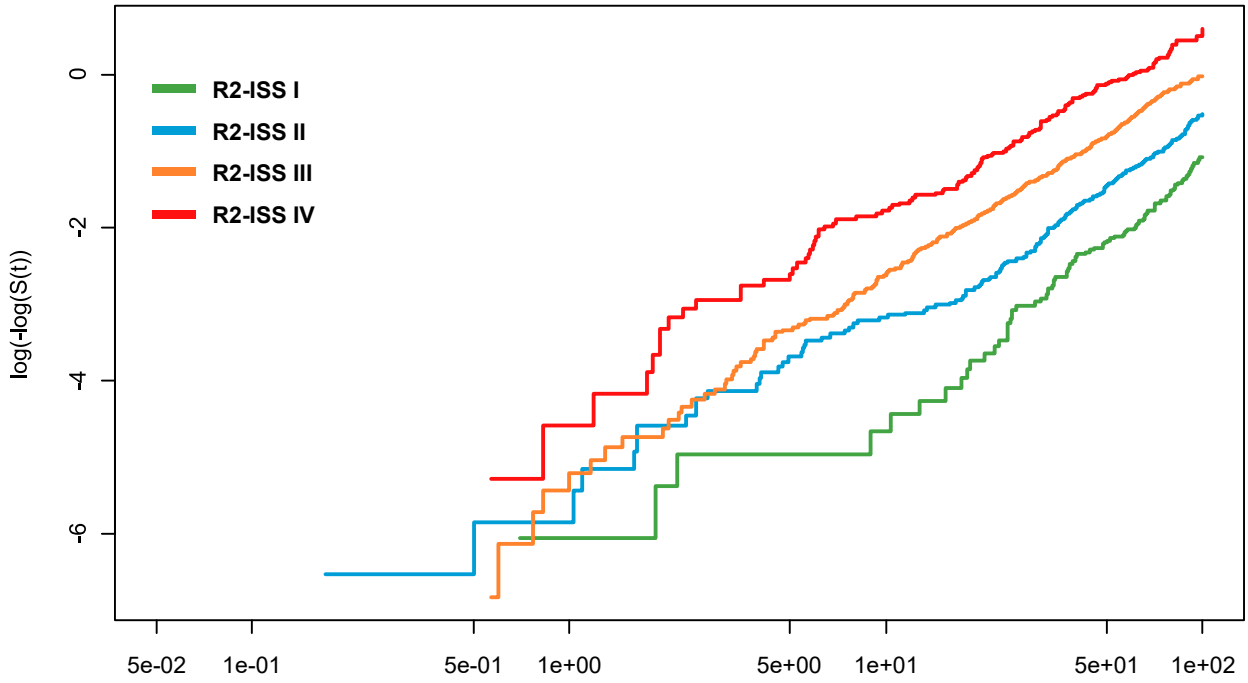


Abbreviations. OS, overall survival; R2-ISS, Second Revision of the International Staging System.

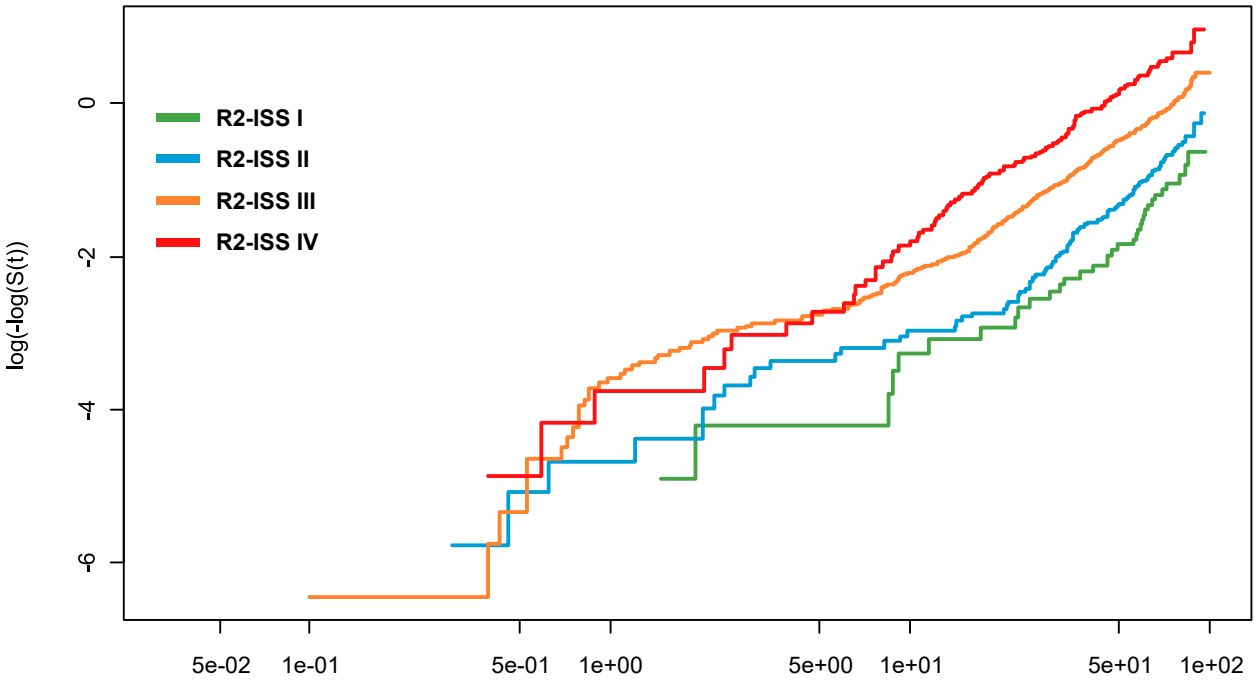
Figure S3. Proportional hazards assessment of the R2-ISS for OS

A log-negative log plot by R2-ISS risk group for OS was performed in the training (Panel a) and validation (Panel b) sets as a visual approach to evaluate the proportional hazards assumption.

S3a. Log-negative log plot by R2-ISS risk group for OS in the training set



S3b. Log-negative log plot by R2-ISS risk group for OS in the validation set

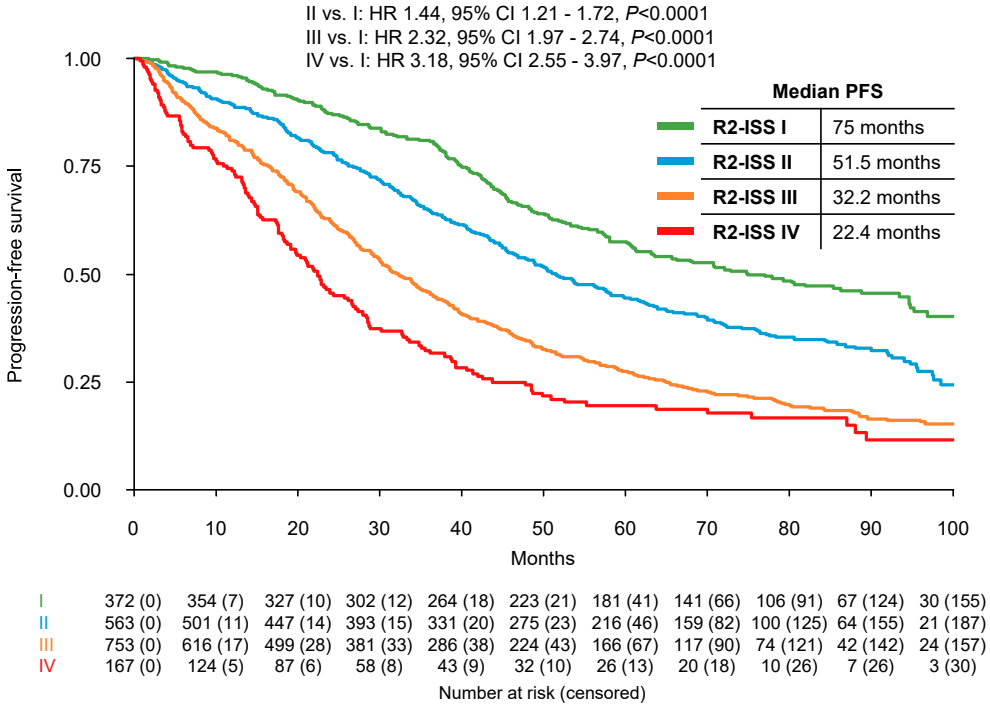


Abbreviations. R2-ISS, Second Revision of the International Staging System; OS, overall survival.

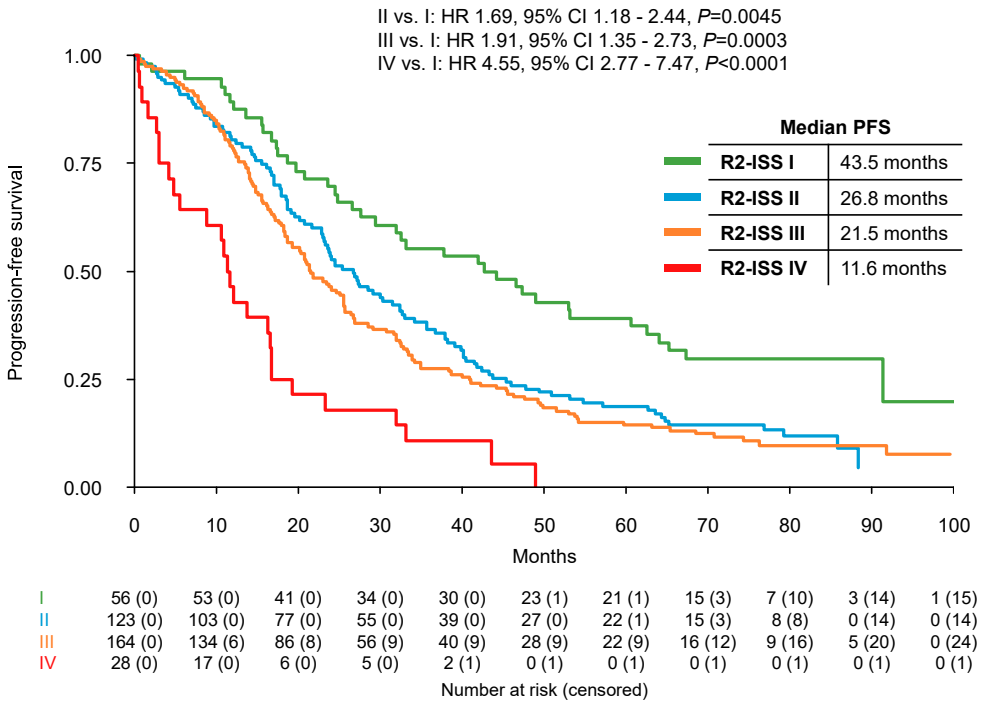
Figure S4. R2-ISS and PFS by transplant eligibility and type of treatment in the training set

Panel a refers to progression-free survival (PFS) in transplant-eligible patients; Panel b refers to PFS in transplant-ineligible patients; Panel c refers to PFS in patients receiving regimens based on immunomodulatory drugs (IMiDs); Panel d refers to PFS in patients receiving regimens based on proteasome inhibitors (PIs); and Panel e refers to PFS in patients receiving regimens based on IMiDs plus PIs.

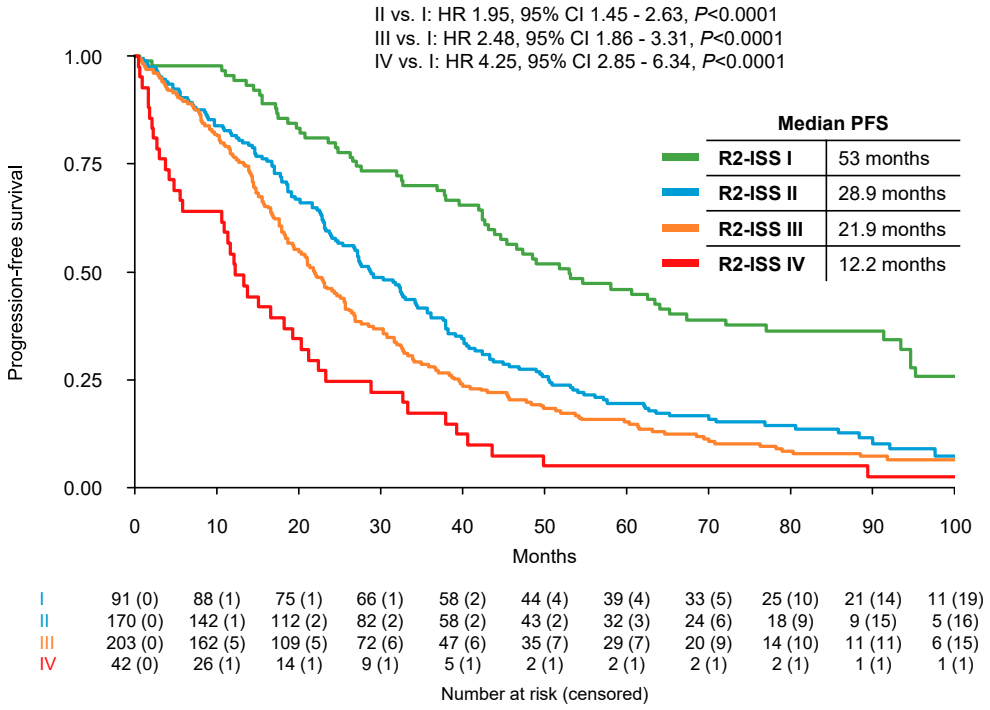
S4a. PFS in transplant-eligible patients



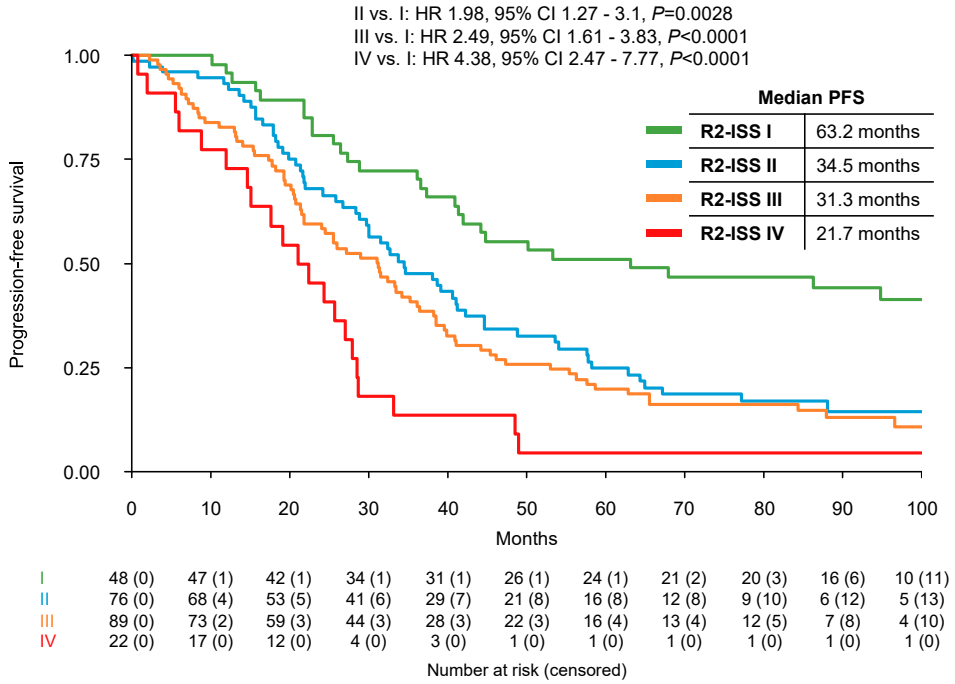
S4b. PFS in transplant-ineligible patients



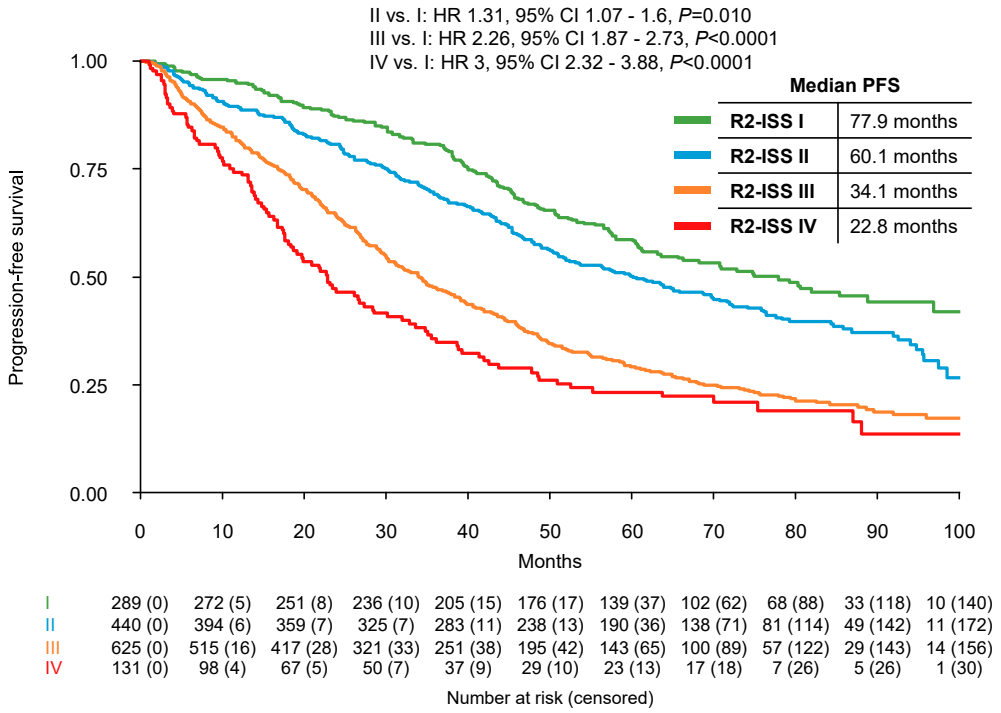
S4c. PFS in patients receiving IMiD-based regimens



S4d. PFS in patients receiving PI-based regimens



S4e. PFS in patients receiving IMiD plus PI-based regimens

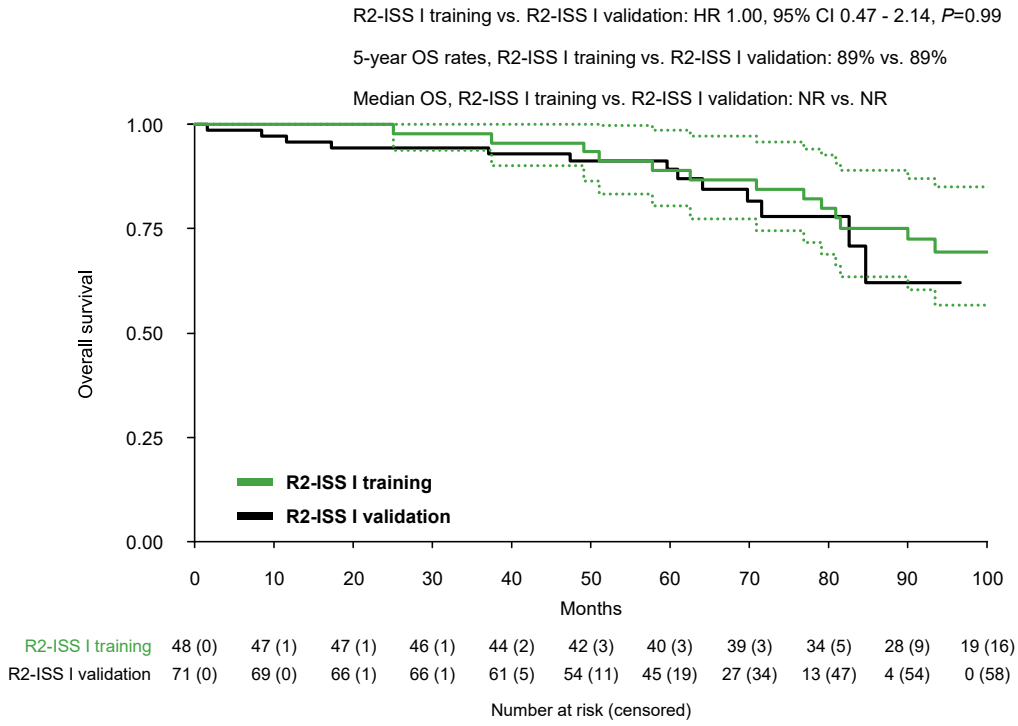


Abbreviations. R2-ISS, Second Revision of the International Staging System; PFS, progression-free survival; IMiDs, immunomodulatory drugs; PIs, proteasome inhibitors; HR, hazard ratio; CI, confidence interval; *P*, *P* value; NR, not reached.

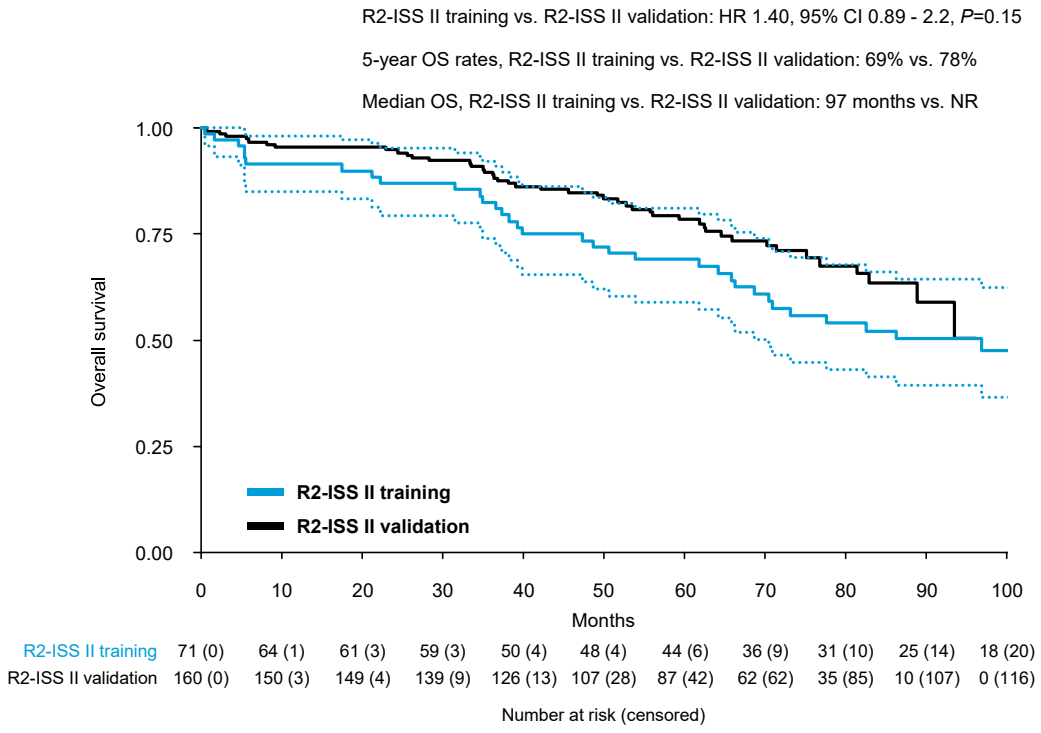
Figure S5. Calibration of the R2-ISS in transplant-eligible patients receiving an IMiD-based treatment

In each panel, the comparison between the same R2-ISS-defined risk subgoup in the training set vs. validation set is shown. Dotted lines refer to the 95% conficence interval of the survival curve in the training set.

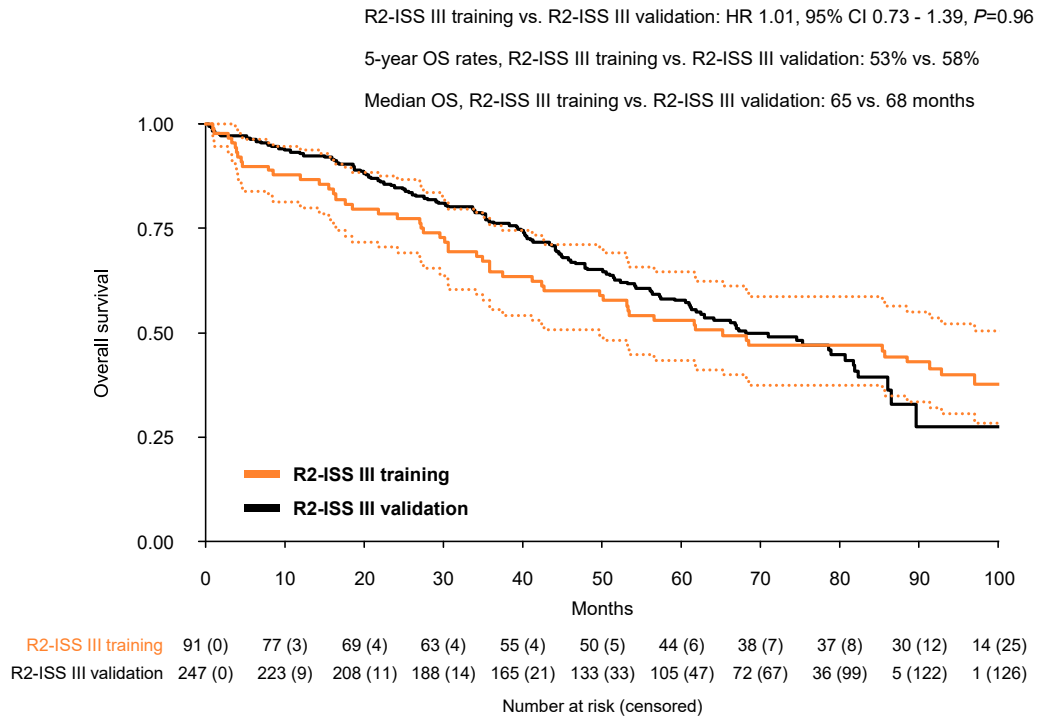
S5a. R2-ISS I



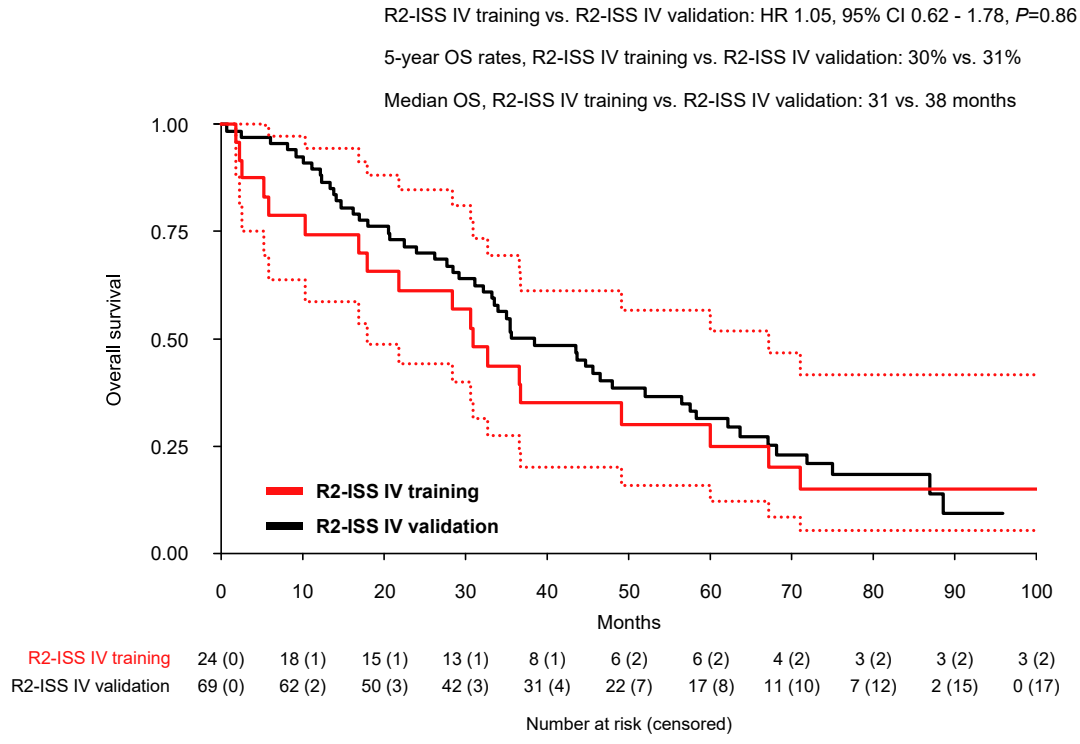
S5b. R2-ISS II



S5c. R2-ISS III



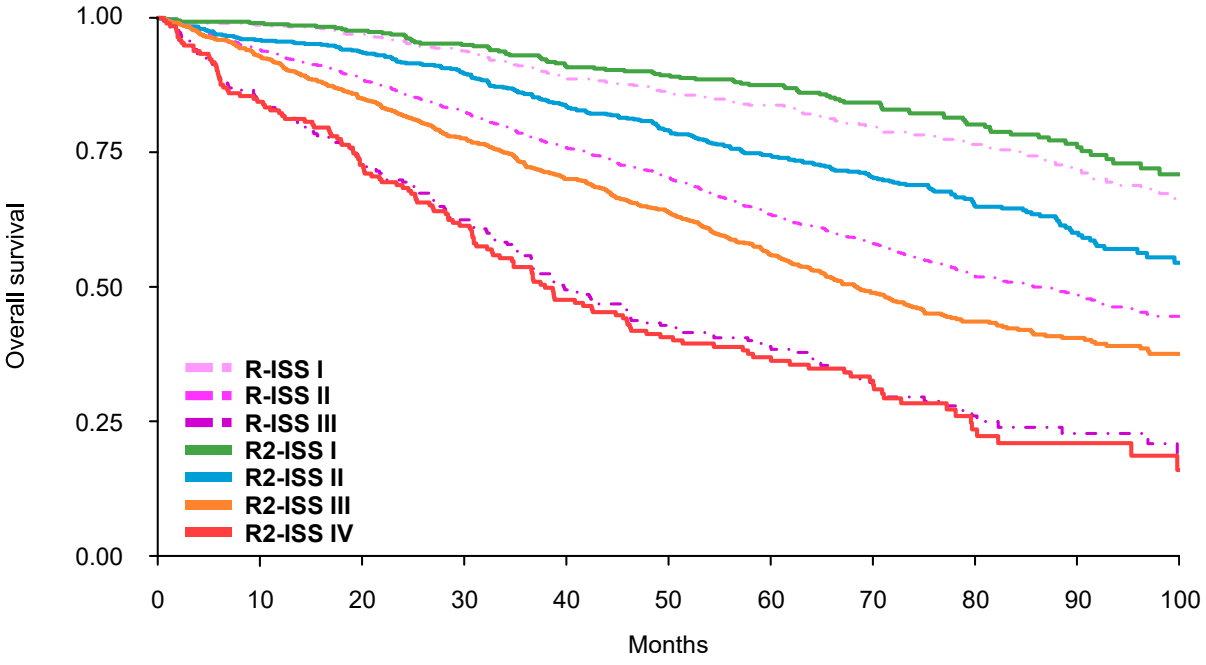
S5d. R2-ISS IV



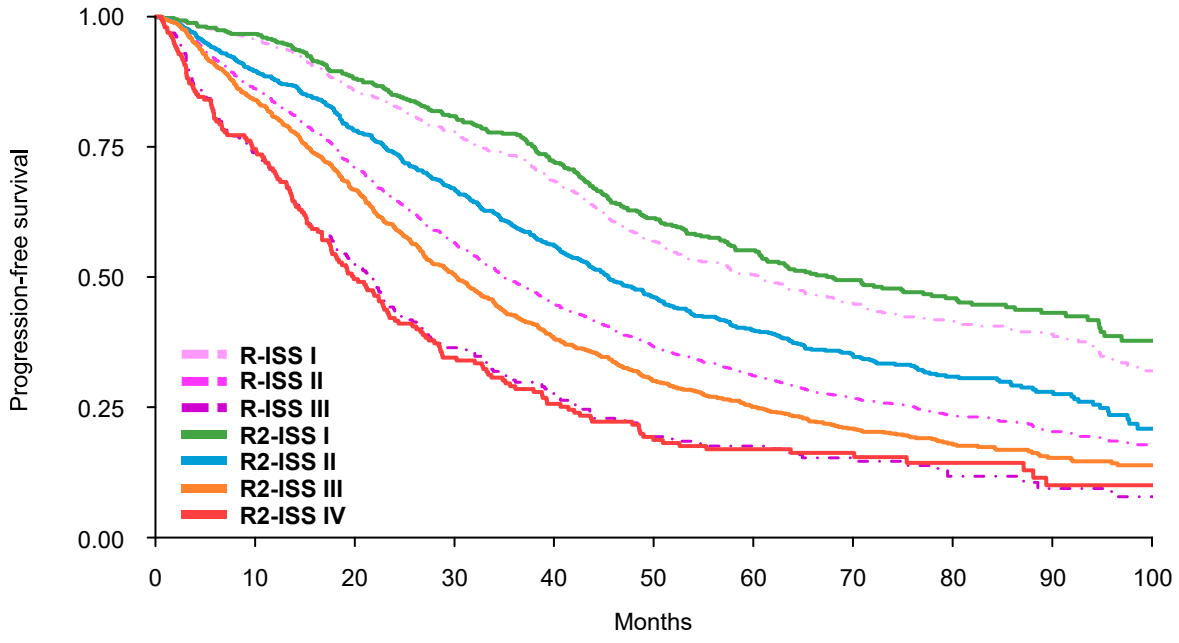
Abbreviations. R2-ISS, Second Revision of the International Staging System; IMiD, immunomodulatory drug; HR, hazard ratio; CI, confidence interval; *P*, *P* value; OS, overall survival; NR, not reached.

Figure S6. OS (Panels a, c) and PFS (Panels b, d) curves in the training (Panels a-b) and validation (Panels c-d) sets according to the R2-ISS, with superimposed R-ISS in the same patient population

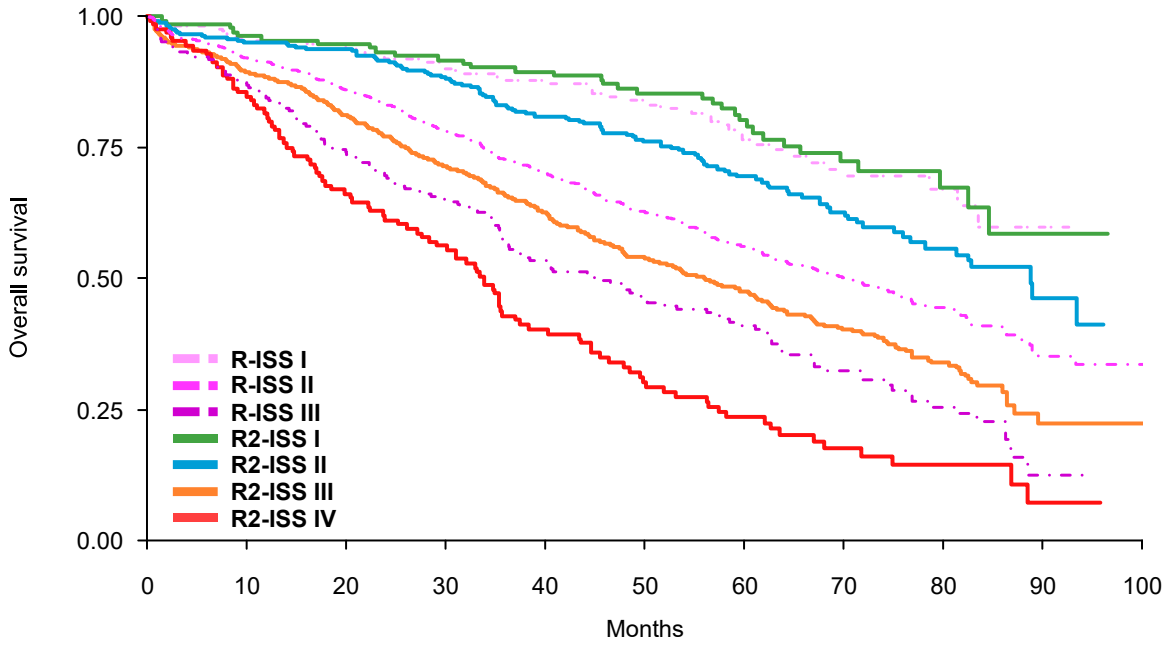
S6a. OS - Training set



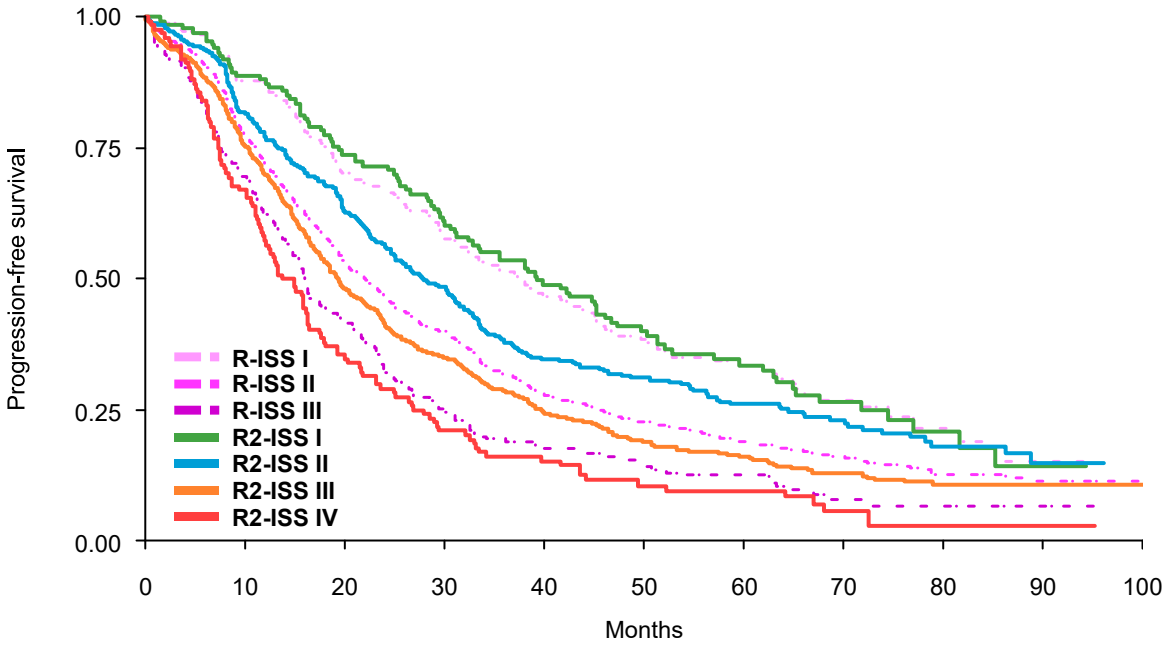
S6b. PFS - Training set



S6c. OS - Validation set



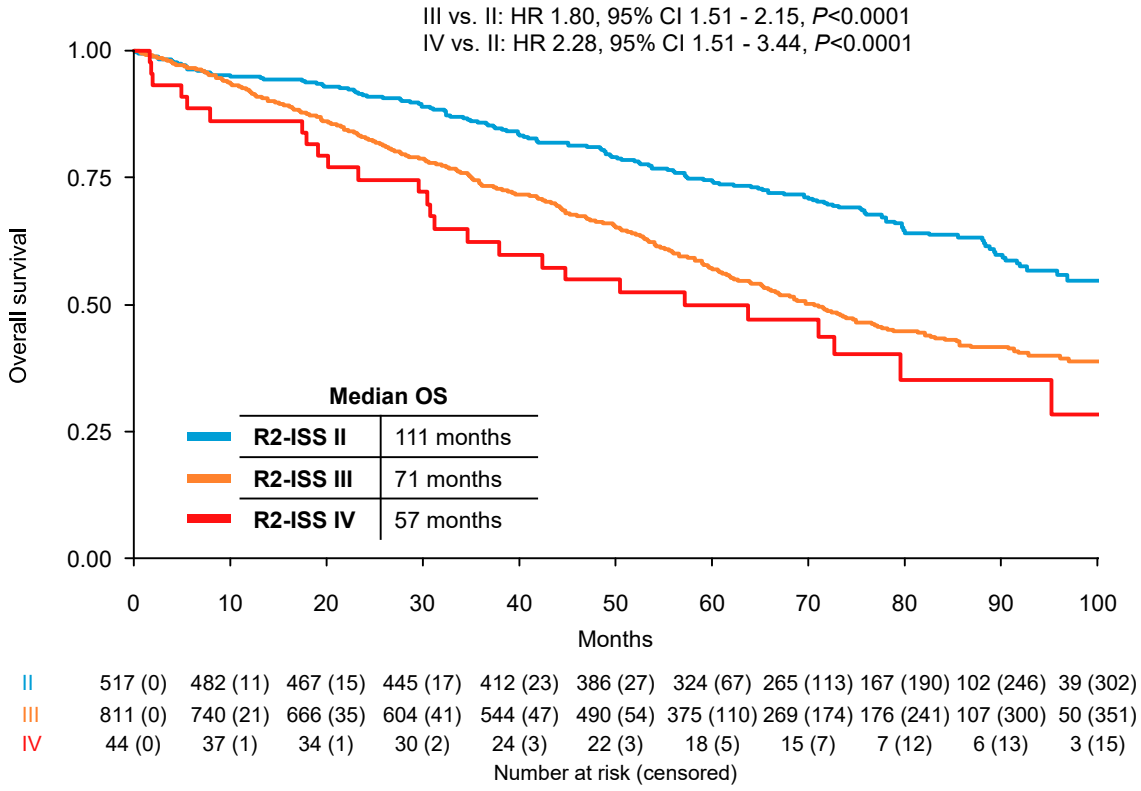
S6d. PFS - Validation set



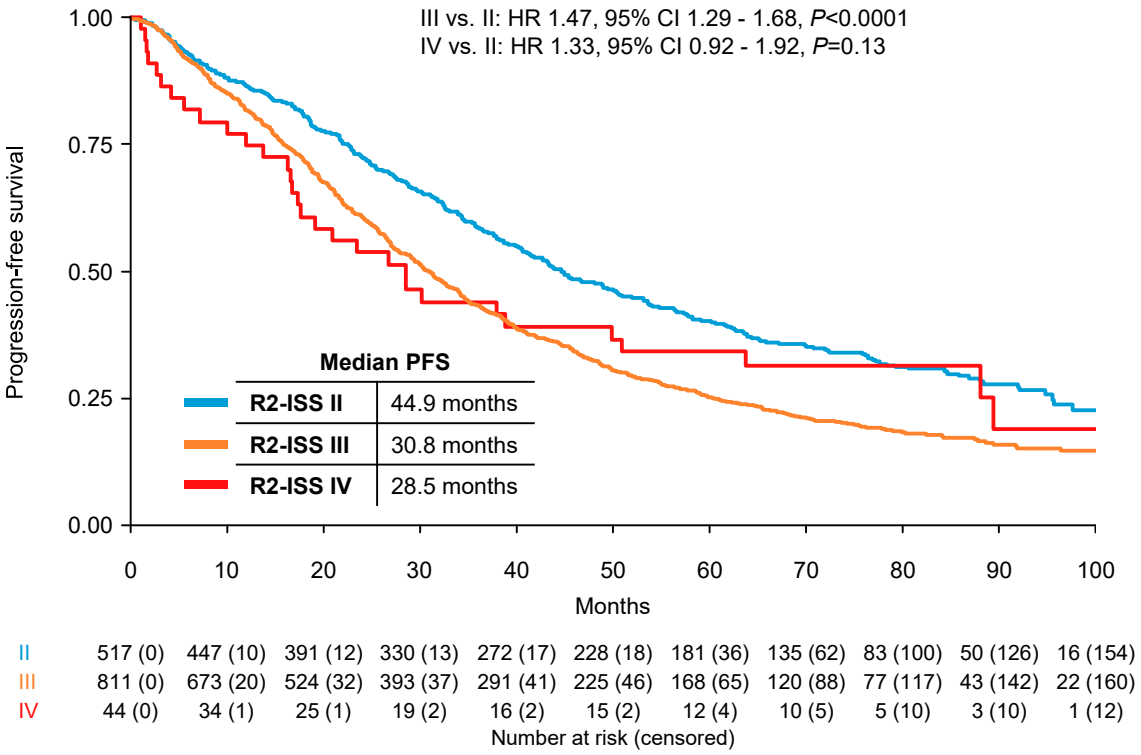
Abbreviations. OS, overall survival; PFS, progression-free survival; R2-ISS, Second Revision of the International Staging System; R-ISS, Revised International Staging System.

Figure S7. OS (Panels a, c) and PFS (Panels b, d) of R-ISS II patients according to the R2-ISS in the training (Panels a-b) and validation (Panels c-d) sets

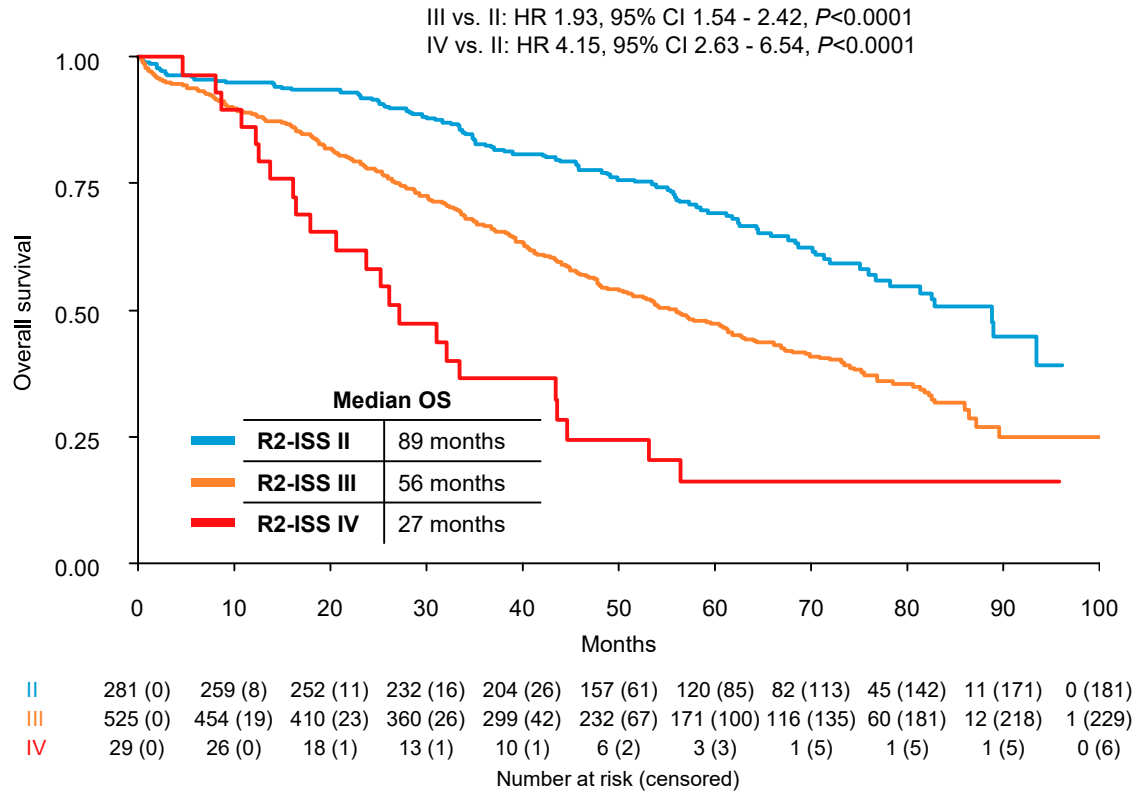
S7a. OS - Training set



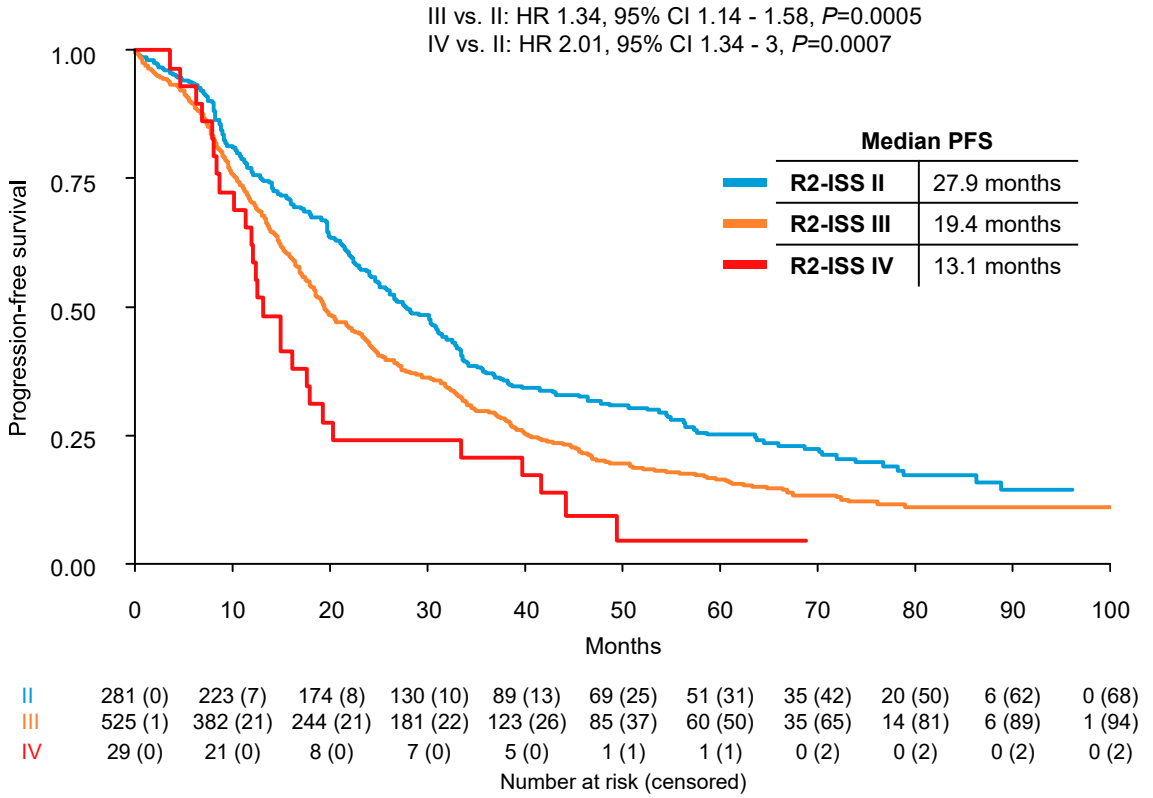
S7b. PFS - Training set



S7c. OS - Validation set

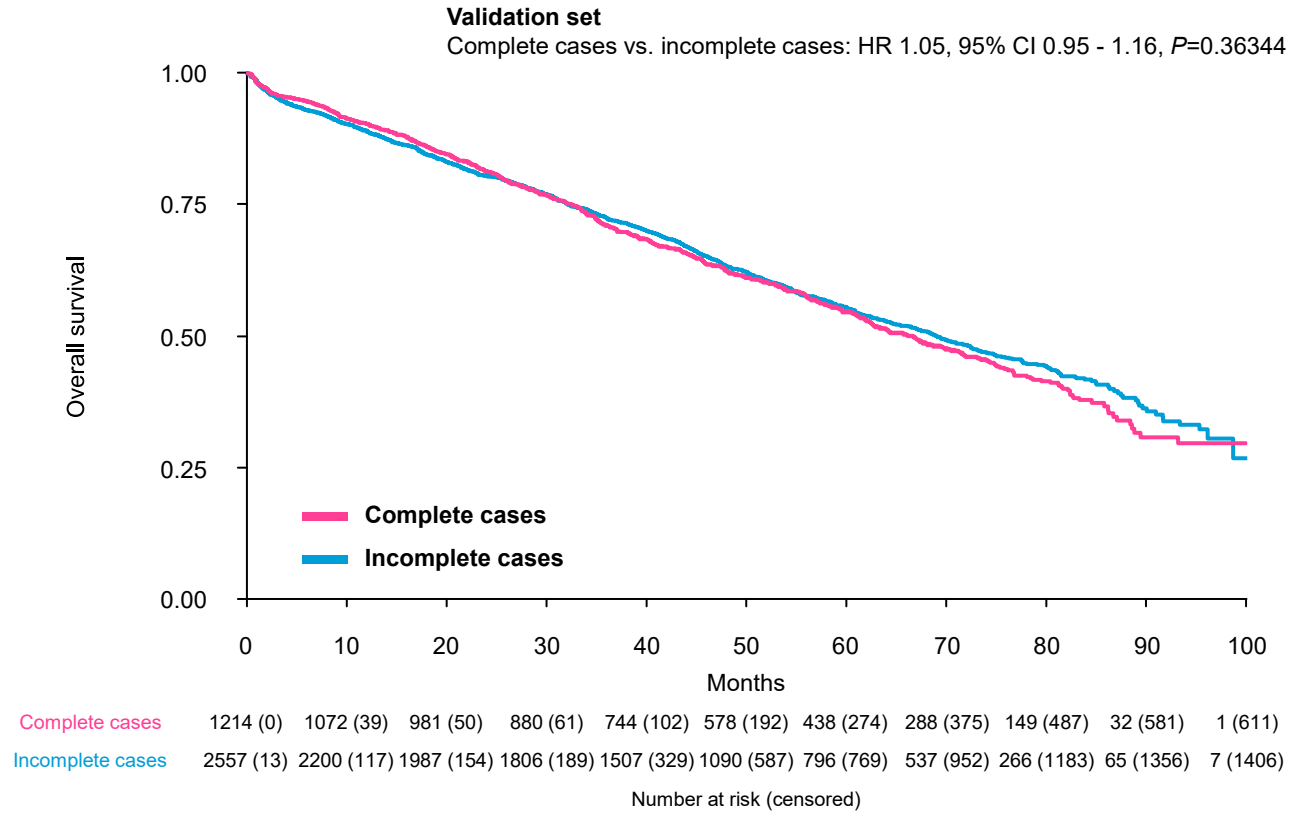


S7d. PFS - Validation set



Abbreviations. OS, overall survival; PFS, progression-free survival; R-ISS II, Revised International Staging System stage II; R2-ISS, Second Revision of the International Staging System; HR, hazard ratio; CI, confidence interval; *P*, *P* value.

Figure S8. OS in complete vs. incomplete cases in the validation set



Abbreviations. OS, overall survival; HR, hazard ratio; CI, confidence interval; *P*, *P* value.

References

1. Greipp PR, San-Miguel J, Dune BGM, et al: International staging system for multiple myeloma. J Clin Oncol 23:3412–3420, 2005
2. Palumbo A, Avet-Loiseau H, Oliva S, et al: Revised international staging system for multiple myeloma: A report from international myeloma working group. J Clin Oncol 33:2863–2869, 2015
3. Levey AS, Coresh J, Greene T, et al: Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 145:247–254, 2006
4. Dimopoulos MA, Kastritis E, Delimpasi S, et al: Multiple myeloma in octogenarians: Clinical features and outcome in the novel agent era. Eur J Haematol 89:10–15, 2012
5. Krejci M, Buchler T, Hajek R, et al: Prognostic factors for survival after autologous transplantation: A single centre experience in 133 multiple myeloma patients. Bone Marrow Transplant 35:159–164, 2005
6. Bachmann F, Schreder M, Engelhardt M, et al: Kinetics of renal function during induction in newly diagnosed multiple myeloma: Results of two prospective studies by the German myeloma study group DSMM. Cancers (Basel) 13:1322, 2021
7. Shah V, Sherborne AL, Walker BA, et al: Prediction of outcome in newly diagnosed myeloma: A meta-analysis of the molecular profiles of 1905 trial patients. Leukemia 32:102–110, 2018
8. Magarotto V, Bringhen S, Offidani M, et al: Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma. Blood 127:1102–1108, 2016
9. Bringhen S, D'Agostino M, Paris L, et al: Lenalidomide-based induction and maintenance in elderly newly diagnosed multiple myeloma patients: updated results of the EMN01 randomized trial. Haematologica 105:1937–1947, 2020
10. Cavo M, Gay F, Beksac M, et al: Autologous haematopoietic stem-cell transplantation versus bortezomib–melphalan–prednisone, with or without bortezomib–lenalidomide–dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): A multicentre, randomised, open-label, phase 3 study. Lancet Haematol 7:e456–e468, 2020
11. Sonneveld P, Dimopoulos MA, Beksac M, et al: Consolidation and maintenance in newly diagnosed multiple myeloma. J Clin Oncol 39:3613–3622, 2021
12. Mateos M-V, Oriol A, Martínez-López J, et al: Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: A randomised trial. Lancet Oncol 11:934–41, 2010
13. Mateos M-V, Oriol A, Martinez-Lopez J, et al: Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. Blood 120:2581–2588, 2012
14. Mateos M-V, Oriol A, Martinez-Lopez J, et al: GEM2005 trial update comparing VMP/VTP as induction in elderly multiple myeloma patients: Do we still need alkylators? Blood 124:1887–1893, 2014
15. Rosiñol L, Oriol A, Teruel AI, et al: Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: A randomized phase 3 PETHEMA/GEM study. Blood 120:1589–1596, 2012
16. Rosiñol Dachs L, Oriol A, Teruel AI, et al: VTD (Bortezomib/thalidomide/dexamethasone) as pretransplant induction therapy for multiple myeloma: Definitive results of a randomized phase 3 PETHEMA/GEM study. Blood 132:Abstract #126 [ASH 2018 60th Meeting], 2018
17. Mateos M-V, Martínez-López J, Hernández M-T, et al: Sequential vs alternating administration of VMP and Rd in elderly patients with newly diagnosed MM. Blood 127:420–425, 2016
18. Palumbo A, Bringhen S, Rossi D, et al: Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: A randomized controlled trial. J Clin Oncol 28:5101–5109, 2010
19. Palumbo A, Bringhen S, Larocca A, et al: Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: Updated follow-up and improved survival. J Clin Oncol 32:634–640, 2014
20. Sonneveld P, Schmidt-Wolf IGH, van der Holt B, et al: Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: Results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol 30:2946–2955, 2012
21. Goldschmidt H, Lokhorst HM, Mai EK, et al: Bortezomib before and after high-dose therapy in myeloma: Long-term results from the phase III HOVON-65/GMMG-HD4 trial. Leukemia 32:383–390, 2018
22. Zweegman S, van der Holt B, Mellqvist U-H, et al: Melphalan, prednisone, and lenalidomide versus melphalan, prednisone, and thalidomide in untreated multiple myeloma. Blood 127:1109–1116, 2016
23. Bringhen S, Petrucci MT, Larocca A, et al: Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: A multicenter, phase 2 study. Blood 124:63–69, 2014
24. Cavo M, Tacchetti P, Patriarca F, et al: Bortezomib with thalidomide plus dexamethasone compared with

thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: A randomised phase 3 study. Lancet 376:2075–2085, 2010
25. Tacchetti P, Pantani L, Patriarca F, et al: Bortezomib, thalidomide, and dexamethasone followed by double autologous haematopoietic stem-cell transplantation for newly diagnosed multiple myeloma (GIMEMA-MMY-3006): Long-term follow-up analysis of a randomised phase 3, open-label study. Lancet Haematol 7:e861–e873, 2020
26. Mai EK, Bertsch U, Dürig J, et al: Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma. Leukemia 29:1721–1729, 2015
27. Goldschmidt H, Mai EK, Dürig J, et al: Response-adapted lenalidomide maintenance in newly diagnosed myeloma: Results from the phase III GMMG-MM5 trial. Leukemia 34:1853–1865, 2020
28. Larocca A, Bringhen S, Petrucci MT, et al: A phase 2 study of three low-dose intensity subcutaneous bortezomib regimens in elderly frail patients with untreated multiple myeloma. Leukemia 30:1320–1326, 2016
29. Gay F, Oliva S, Petrucci MT, et al: Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: A randomised, multicentre, phase 3 trial. Lancet Oncol 16:1617–1629, 2015
30. Palumbo A, Gay F, Falco P, et al: Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients. J Clin Oncol 28:800–807, 2010
31. Gay F, Magarotto V, Crippa C, et al: Bortezomib induction, reduced-intensity transplantation, and lenalidomide consolidation-maintenance for myeloma: updated results. Blood 122:1376–1383, 2013
32. Palumbo A, Cavallo F, Gay F, et al: Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med 371:895–905, 2014
33. Jackson GH, Davies FE, Pawlyn C, et al: Response-adapted intensification with cyclophosphamide, bortezomib, and dexamethasone versus no intensification in patients with newly diagnosed multiple myeloma (Myeloma XI): A multicentre, open-label, randomised, phase 3 trial. Lancet Haematol 6:e616–e629, 2019
34. Jackson GH, Davies FE, Pawlyn C, et al: Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 20:57–73, 2019
35. Jackson GH, Pawlyn C, Cairns DA, et al: Optimising the value of immunomodulatory drugs during induction and maintenance in transplant ineligible patients with newly diagnosed multiple myeloma: Results from Myeloma XI, a multicentre, open-label, randomised, phase III trial. Br J Haematol 192:853–868, 2021
36. Jackson GH, Davies FE, Pawlyn C, et al: Lenalidomide before and after autologous stem cell transplantation for transplant-eligible patients of all ages in the randomized, phase III, Myeloma XI trial. Haematologica 106:1957–1967, 2021
37. Jackson GH, Pawlyn C, Cairns DA, et al: Carfilzomib, lenalidomide, dexamethasone, and cyclophosphamide (KRdc) as induction therapy for transplant-eligible, newly diagnosed multiple myeloma patients (Myeloma XI+): Interim analysis of an open-label randomised controlled trial. PLoS Med 18:e1003454, 2021