

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

**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, t(4;14) 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.

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## ASSOCIATED CONTENT

### Data Supplement

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

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## 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.<sup>1</sup> 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).<sup>2,3</sup>

The R-ISS takes into account ISS (which integrates  $\beta_2$ -microglobulin levels and serum albumin to reflect tumor

mass and renal function),<sup>4</sup> 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)],<sup>5</sup> and serum lactate dehydrogenase (LDH) levels.<sup>6,7</sup> 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 ( $\geq$  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.<sup>2</sup>

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 ( $\geq$  four copies of 1q), which were not included in the R-ISS, proved to be independent poor prognostic factors in NDMM.<sup>8-10</sup> 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.<sup>8</sup>

The European Myeloma Network (EMN), under the umbrella of the European Union–funded HARMONY project,<sup>11</sup> 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,<sup>12</sup> EMN01,<sup>13,14</sup> RV-MM-EMN-441,<sup>15</sup> MM-RV-PI-209,<sup>16</sup> RV-MM-PI-114,<sup>17,18</sup> GIMEMA-MM-03-05,<sup>19,20</sup> 26866138MMY2069,<sup>21</sup> HOVON-

65/GMMG-HD4,<sup>22,23</sup> MM-BO2005,<sup>24,25</sup> GEM05MENOS65,<sup>26,27</sup> EMN02/HO95,<sup>28,29</sup> GEM05MAS65,<sup>30-32</sup> GEM2010MAS65,<sup>33</sup> HOVON-87/NMSG-18,<sup>34</sup> GMMG-MM5,<sup>35,36</sup> and UK National Cancer Research Institute [UK NCRI] Myeloma XI<sup>37-41</sup>). 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<sup>42</sup> in compliance with the General Data Protection Regulation, harmonized and transformed using an Observational Medical Outcomes Partnership Common Data Model,<sup>43</sup> 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<sup>2,9</sup> (in the training set) or by molecular methods validated against FISH<sup>8</sup> (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  $\geq$  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+.<sup>44</sup>

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<sup>45</sup> 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  $\nu$  F), transplant eligibility (TE  $\nu$  NTE), and type of treatment (PIs  $\nu$  IMiDs  $\nu$  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.<sup>46</sup> The discrimination ability of a model including  $\geq$  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,<sup>47</sup> 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  $\leq$  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  $\leq$  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  $\nu$  I and HR, 1.55 [95% CI, 1.42 to 1.69] for ISS II  $\nu$  I); del(17p) (HR, 1.74 [95% CI, 1.56 to 1.94]  $\nu$  no del(17p)); LDH  $>$  upper limit of normal ([ULN]; HR, 1.66 [95% CI, 1.50 to 1.83]  $\nu$  LDH  $\leq$  ULN); t(4;14) (HR, 1.56 [95% CI, 1.40 to 1.74]  $\nu$  no t(4;14)); 1q+ (HR, 1.45 [95% CI, 1.29 to 1.63]  $\nu$  no 1q+); t(14;16) (HR, 1.34 [95% CI, 1.09 to 1.65]  $\nu$  no t(14;16)); Eastern Cooperative Oncology Group performance status (ECOG PS)  $>$  1 (HR, 1.32 [95% CI, 1.20 to 1.44]  $\nu$  ECOG PS  $\leq$  1); immunoglobulin A (IgA) heavy chain (HR, 1.23 [95% CI, 1.14 to 1.34]  $\nu$  no IgA); and creatinine clearance  $\leq$  45 mL/min (HR, 1.11 [95% CI, 1.01 to 1.23]  $\nu$  creatinine clearance  $>$  45 mL/min).

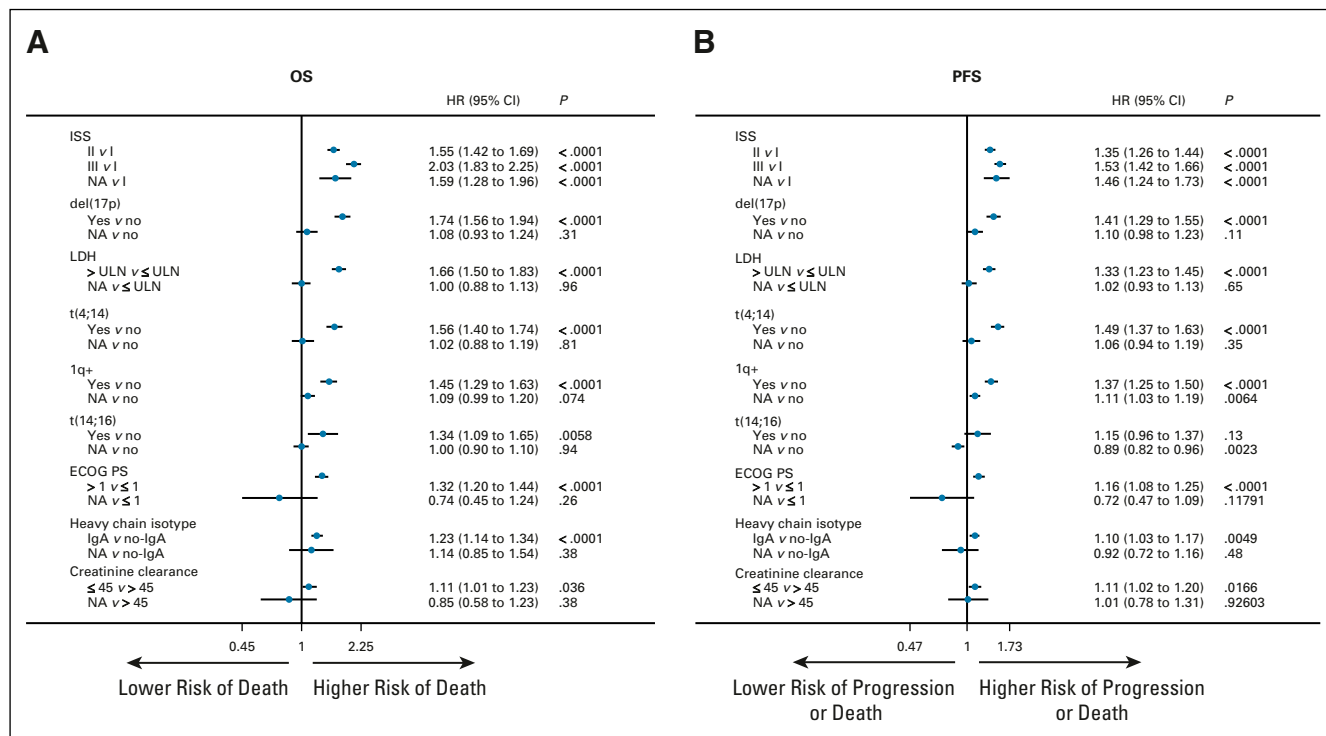
The statistically significant predictors for PFS in multivariate analysis were ISS stage (HR, 1.53 [95% CI, 1.42 to 1.66] for

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 <sup>a</sup>
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.

<sup>a</sup>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.

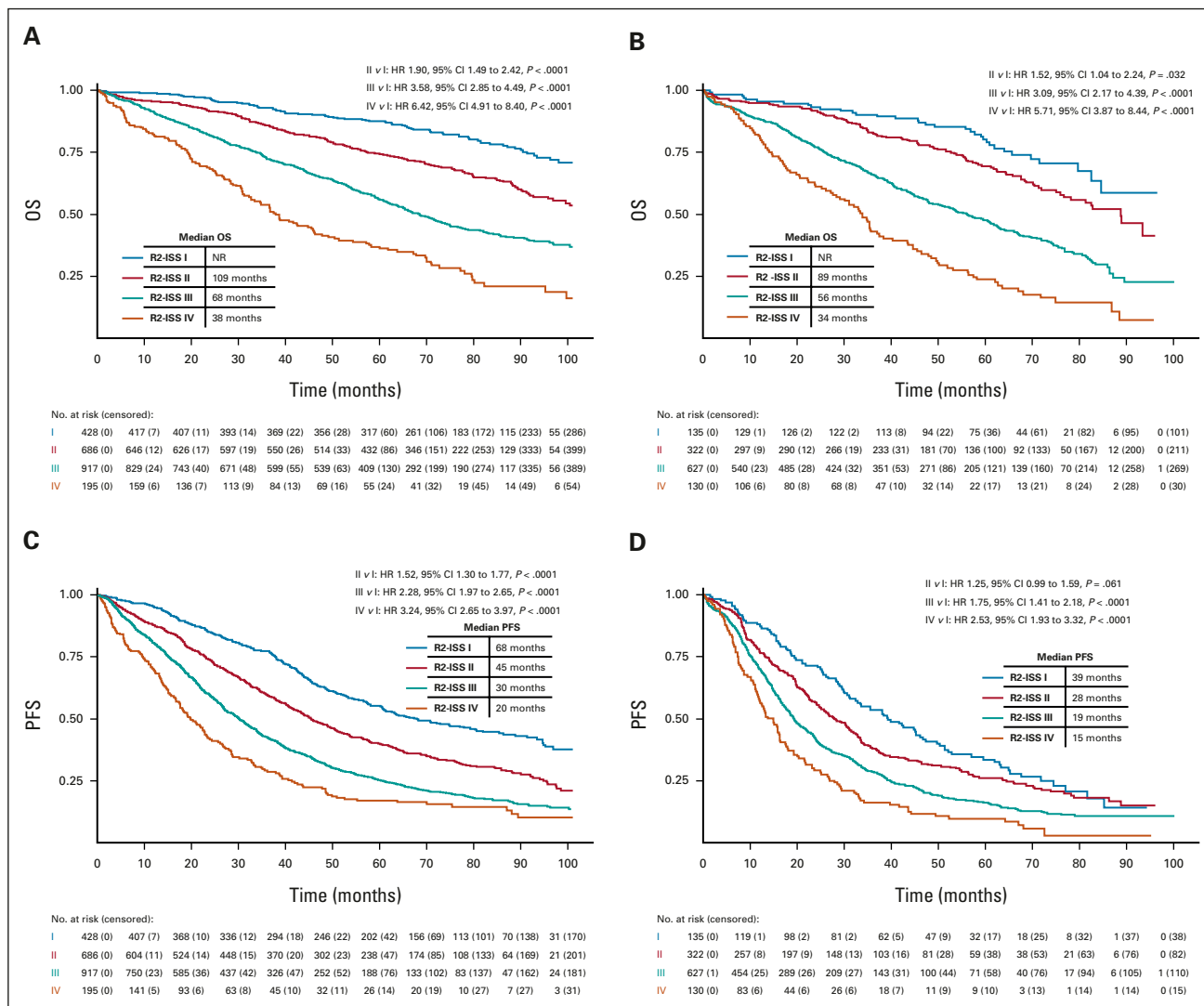
### DISCUSSION

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,<sup>2</sup> the R2-ISS adds 1q+ to the score, and its calculation takes into account the prognostic significance of the coexistence of several CA.

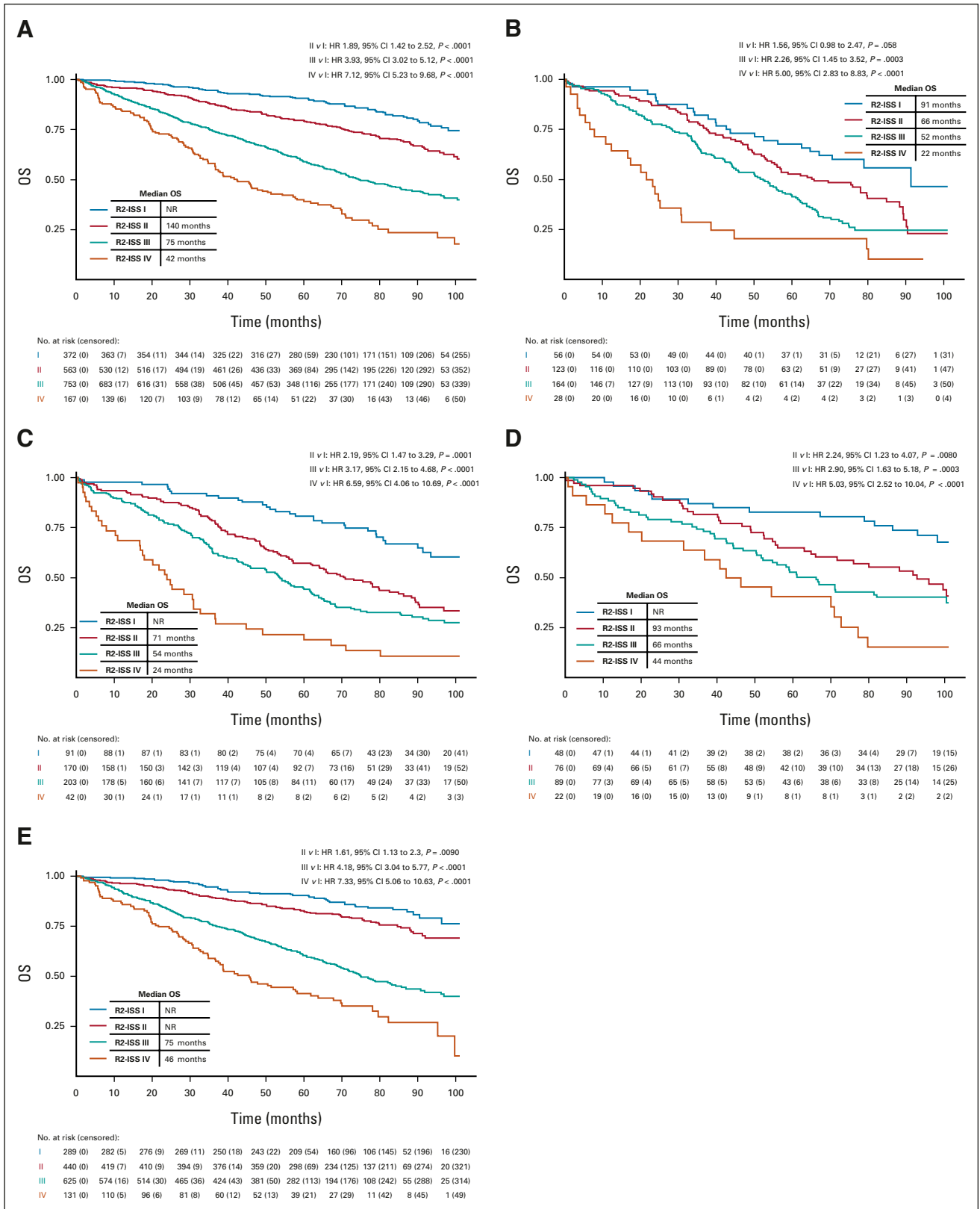
Of note, 1q+ is a very common finding in NDMM, with approximately 40% of patients presenting with this abnormality.<sup>44</sup> Although this variable was missing in many older trials included in this analysis, the multivariate analysis on the available patients (2,770 patients in the training cohort 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.<sup>48,49</sup> 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.<sup>48,49</sup>

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)<sup>2</sup> 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,<sup>50</sup> and the validated scores to define patient frailty should be explored in combination with the R2-ISS.<sup>50</sup>

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,<sup>51</sup> and triplets and quadruplets including monoclonal antibodies<sup>52-54</sup>). 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  $\beta$ 2-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.<sup>55</sup> 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,<sup>56,57</sup> TP53 mutations,<sup>58,59</sup> 1p32 deletion,<sup>60</sup> lambda light-chain translocations,<sup>61</sup> extramedullary disease,<sup>62,63</sup> and Myc deregulation<sup>64</sup>) 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) ( $\geq$  four copies of 1q) may further improve the risk stratification.<sup>58,65,66</sup>

Moreover, molecular data (next-generation sequencing<sup>58,59</sup> and/or gene-expression profiling)<sup>67</sup> 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.<sup>68</sup> 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,<sup>69</sup> 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

<sup>1</sup>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

<sup>2</sup>Leeds Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom

<sup>3</sup>Instituto de Investigación del Hospital Universitario 12 de Octubre, Madrid, Spain

<sup>4</sup>Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

<sup>5</sup>University Hospital Heidelberg, Internal Medicine V and National Center for Tumor Diseases (NCT), Heidelberg, Germany

<sup>6</sup>Institute of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

<sup>7</sup>IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli," Bologna, Italy

<sup>8</sup>Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy

<sup>9</sup>Complejo Asistencial Universitario de Salamanca/IBSAL/CIC/Ciberonc, Salamanca, Spain

<sup>10</sup>Dipartimento di Fisica e Astronomia, Università di Bologna, Bologna, Italy

<sup>11</sup>Department of Hematology, Amsterdam UMC, Cancer Center Amsterdam, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

<sup>12</sup>University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom

<sup>13</sup>Asklepios Tumorzentrum Hamburg, AK Altona and AK St Georg, Hamburg, Germany

<sup>14</sup>Hospital Clinic, IDIBAPS, Barcelona, Spain

<sup>15</sup>HOVON Data Center, Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

<sup>16</sup>Department of Hematology, University Clinic Essen, Essen, Germany

<sup>17</sup>The Institute of Cancer Research, London, United Kingdom and The Royal Marsden Hospital, London, United Kingdom

<sup>18</sup>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

<sup>19</sup>Clinica 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](mailto:mattia.dagostino@unito.it).

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## 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](mailto: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

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**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**

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**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, Oncoceptides, 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:** Oncoceptides, 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, Oncoceptides, GlaxoSmithKline, Amgen, AbbVie, Bristol Myers Squibb/Celgene, Roche, Genzyme

**Joan Bladé Creixenti**

**Honoraria:** Janssen, Celgene, Amgen, Takeda, Oncoceptides

**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, Oncoceptides, bluebird bio, Pfizer

**Sonja Zweegman**

**Consulting or Advisory Role:** Janssen-Cilag (Inst), Takeda (Inst), Celgene (Inst), Sanofi (Inst), Oncoceptides (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, Oncoceptides, GlaxoSmithKline, Sanofi, Karyopharm Therapeutics

**Consulting or Advisory Role:** Janssen-Cilag, Bristol Myers Squibb, Amgen, Takeda, Oncoceptides, GlaxoSmithKline, Sanofi, Karyopharm Therapeutics

**Gordon Cook**

**Honoraria:** Takeda, Janssen-Cilag, Celgene, Karyopharm Therapeutics, Bristol Myers Squibb, Amgen, Oncoceptides

**Consulting or Advisory Role:** Janssen, Bristol Myers Squibb, Amgen, Takeda, Karyopharm Therapeutics, Oncoceptides

**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 Boccardo**

**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)

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