

Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group

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A B S T R A C T

Purpose

The clinical outcome of multiple myeloma (MM) is heterogeneous. A simple and reliable tool is needed to stratify patients with MM. We combined the International Staging System (ISS) with chromosomal abnormalities (CA) detected by interphase fluorescent in situ hybridization after CD138 plasma cell purification and serum lactate dehydrogenase (LDH) to evaluate their prognostic value in newly diagnosed MM (NDMM).

Patients and Methods

Clinical and laboratory data from 4,445 patients with NDMM enrolled onto 11 international trials were pooled together. The K-adaptive partitioning algorithm was used to define the most appropriate subgroups with homogeneous survival.

Results

ISS, CA, and LDH data were simultaneously available in 3,060 of 4,445 patients. We defined the following three groups: revised ISS (R-ISS) I (n = 871), including ISS stage I (serum β_2 -microglobulin level < 3.5 mg/L and serum albumin level \geq 3.5 g/dL), no high-risk CA [del(17p) and/or t(4;14) and/or t(14;16)], and normal LDH level (less than the upper limit of normal range); R-ISS III (n = 295), including ISS stage III (serum β_2 -microglobulin level > 5.5 mg/L) and high-risk CA or high LDH level; and R-ISS II (n = 1,894), including all the other possible combinations. At a median follow-up of 46 months, the 5-year OS rate was 82% in the R-ISS I, 62% in the R-ISS II, and 40% in the R-ISS III groups; the 5-year PFS rates were 55%, 36%, and 24%, respectively.

Conclusion

The R-ISS is a simple and powerful prognostic staging system, and we recommend its use in future clinical studies to stratify patients with NDMM effectively with respect to the relative risk to their survival.

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INTRODUCTION

Multiple myeloma (MM) is a heterogeneous disease, with survival duration ranging from a few months to more than 10 years. New, simple, and more robust biomarkers are needed to better dissect different disease categories within MM associated with different outcomes.¹

The International Staging System (ISS) is a simple risk stratification algorithm based on two parameters; high serum β_2 -microglobulin level reflects high tumor mass and reduced renal function, and low serum albumin in MM is mainly caused by inflammatory cytokines such as interleukin-6 secreted by the myeloma microenvironment. The ISS score, defined in 2005, identifies three patient

groups with different prognoses; the median overall survival (OS) was 62 months in the ISS stage I, 44 months in the ISS stage II, and 29 months in the ISS stage III groups ($P < .001$).²

Chromosomal abnormalities (CA) detected by interphase fluorescent in situ hybridization (iFISH) are a key element to define the biologic features of MM.³ In newly diagnosed MM (NDMM), standard-risk disease is characterized by the absence of del(17p), translocation t(4;14)(p16;q32), or translocation t(14;16)(q32;q23) and is associated with a median OS of 50.5 months, whereas high-risk disease is characterized by the presence of at least one of the previously mentioned abnormalities and is associated with a median OS of 24.5 months ($P < .001$).⁴

Serum lactate dehydrogenase (LDH) is another relevant biomarker in MM. LDH level above the upper limit of normal denotes an increased disease aggressiveness and suggests high proliferation rate and/or the presence of tumor mass, in particular extramedullary and extraosseous disease.⁵⁻⁹ Studies performed before the availability of novel agents showed that high LDH levels were associated with shorter OS.⁵ Also in the era of novel agents, LDH confirmed its impact on survival.⁶

To improve the predictive value of these risk factors evaluated per se, different combinations have been tested. Several studies that combined ISS stage and CA [mainly translocation t(4;14) and del(17p)] identified the following three risk categories: a low-risk group with a 5-year OS rate of a 60% to 70%; an intermediate-risk group with a 5-year OS rate of 40% to 60%; and a high-risk group with a 5-year OS rate of 15% to 40%.¹⁰⁻¹² Another study that combined ISS, CA, and LDH data defined four risk categories. In the very low-risk category, the 2-year OS rate was 93%; by contrast, in the very high-risk category, the 2-year OS rate was 55%, (Appendix Table A1, online only).¹³

These data strongly suggest the need for combining these prognostic factors to better stratify patients into homogeneous survival subgroups. Most of the data currently available were obtained in young patients who received autologous stem-cell transplantation (ASCT), with limited evaluation in elderly patients and patients ineligible for high-dose therapy. Here, we propose a simple model including ISS, CA, and LDH data to define subgroups of patients with different prognosis to better allow stratifications on clinical trials and data comparisons across studies. We assessed this new algorithm, the revised ISS (R-ISS), in 3,060 young and elderly patients with NDMM.

PATIENTS AND METHODS

Patients

A total of 4,445 patients with NDMM were enrolled onto 11 international, multicenter clinical trials, from 2005 to 2012 (Appendix Table A2, online only). The results of these trials were previously reported (Clinical Trials.gov identifiers: NCT01346787, NCTC00551928, NCT01091831, NCT01093196, NCT01190787, NCT01063179, NCT01134484, NCT00461747, NCT00200681; Eudract: 2005-004714-32; Netherlands Trial Register: NTR213).¹⁴⁻²⁴ Patients gave written informed consent before entering the source trials, which were performed in accordance with the Declaration of Helsinki.

All patients received new drugs (immunomodulatory agents [IMiDs] or proteasome inhibitors [PIs]) in association with conventional chemotherapy as up-front treatment or incorporated into pretransplantation induction or post-transplantation maintenance strategies, except for the patients enrolled onto the Intergroupe Français du Myélome 2005-01 trial who were randomly assigned to vincristine, doxorubicin, and dexamethasone (VAD) induction and to VAD plus dexamethasone, cyclophosphamide, etoposide, and cisplatin before ASCT (Appendix Table A3, online only).

Baseline data collected included the following: age, sex, ISS stage, CA detected by iFISH, and serum LDH level. Data about ISS stage, CA by FISH, and serum LDH were simultaneously available in 3,060 of 4,445 patients. The primary end point was OS, defined as the time from start of treatment until death as a result of any cause or until the last date the patient was known to be alive. The secondary end point was progression-free survival (PFS), defined as the time from start of treatment until progression or death as a result of any cause or until the last date the patient was known to be progression free.

ISS, CA, and LDH Analyses

ISS stage I was defined as serum β_2 -microglobulin level less than 3.5 mg/L and serum albumin level \geq 3.5 g/dL. ISS stage II included all patients

with neither stage I nor stage III disease. ISS stage III was defined as serum β_2 -microglobulin level \geq 5.5 mg/L, irrespective of serum albumin level.²

Bone marrow plasma cells (BMPCs) for iFISH analyses were enriched using anti-CD138-coated magnetic MicroBeads and AutoMACS Pro Separator (Miltenyi Biotech, San Diego, CA) following manufacturer's instructions. BMPCs were then fixed in Carnoy's solution and stored at -20°C . Slides for iFISH were prepared using probes purchased from Cytocell (Cambridge, United Kingdom), Kreatech (Buffalo Grove, IL), and Vysis (Des Plaines, IL), according to manufacturer's instructions. The routine panel included baseline evaluation of del(13), del(17p), and immunoglobulin H translocations. Nuclei were analyzed using a fluorescent light microscope. One hundred to 200 BMPC nuclei from each sample were scored. Del(17p), translocation t(4;14), and translocation t(14;16) detected by iFISH were considered high-risk CA. Patients were considered positive for a given CA when it was present in a percentage higher than the cutoff threshold, defined by each local laboratory. Details of interlaboratory variability are reported in the Appendix (online only).

Serum LDH level was recorded at baseline and classified as normal or high according to the local laboratory definition of normal range. High LDH was defined as a serum level greater than the upper limit of normal range; normal LDH was defined as a serum level less than the upper limit of normal (Table 1).

Statistical Analysis

An explorative analysis of the 3,060 patients for whom ISS, CA, and LDH data were simultaneously available was conducted. K-adaptive partitioning,²⁵ dedicated to censored survival data (minimax-based partitioning rule by log-rank test), was used for ISS/CA/LDH grouping; this routine gave an optimal number of three subgroups (R-ISS I, II, and III). The OS and PFS curves were estimated using the Kaplan-Meier method and compared using the log-rank test. OS and PFS were then analyzed through the Cox proportional hazards model, comparing the following risk factors by the Wald test: age at diagnosis (\leq v $>$ 65 years), sex (male v female), iFISH (high-risk v standard-risk CA), LDH (high v normal), ISS stage (II v I and III v I), and R-ISS grouping as defined by the recursive partitioning procedure. The effects of the baseline features (age, sex, and R-ISS) were also assessed by the multivariable Cox

Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2 -microglobulin < 3.5 mg/L, serum albumin \geq 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2 -microglobulin \geq 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

model; as in the univariable analysis, the R-ISS stage was treated as a time-dependent variable. Subgroup analyses of PFS and OS were performed to confirm the effect of R-ISS in different subgroups of patients (ie, in patients older and younger than 65 years of age and in patients receiving or not receiving ASCT, PI, or IMiDs). Patients characteristics were tested using the Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. All reported *P* values were two-sided, at the conventional 5% significance level. Data were analyzed as of December 2014 by R 3.0.1 package kaps (www.r-project.org) and IBM SPSS 21.0.0 (Chicago, IL).

RESULTS

Patient Characteristics and Treatments

Median age was 62 years (range, 18 to 91 years); 65% of patients were \leq 65 years old, and 35% were older than age 65 years. In the overall population of 4,445 patients, 60% received ASCT (most of these patients were \leq 65 years old), 44% received PIs, and 66% received IMiDs; only 5% of patients did not receive any novel agent up front (Table 2). Patient characteristics and treatments of the overall population were similar when compared with the 3,060 patients with ISS, CA, and LDH data available. Of note, of 1,171 patients with ISS stage I, 26% had high-risk CA and/or high LDH levels. Of 715 patients

Characteristic	No. of Patients (%)	
	Total (N = 4,445)	Evaluable (n = 3,060)
Age, years	2,872 (65)	2,080 (68)
\leq 65	1,573 (35)	980 (32)
$>$ 65		
Sex		
Male	2,393 (54)	1,652 (54)
Female	2,050 (46)	1,408 (46)
Missing	2	—
HR-CA by iFISH		
No	2,718 (61)	2,337 (76)
Yes	851 (19)	723 (24)
Missing	876 (20)	—
ISS stage		
I	1,615 (36)	1,171 (38)
II	1,630 (37)	1,174 (38)
III	987 (22)	715 (24)
Missing	213 (5)	—
LDH level		
Normal	3,443 (77)	2,653 (87)
High	530 (12)	407 (13)
Missing	472 (11)	—
Treatment		
ASCT	2,666 (60)	1,998 (65)
No ASCT	1,779 (40)	1,062 (35)
Proteasome inhibitors	1,971 (44)*	1,345 (44)†
Immunomodulatory agents	2,954 (66)*	2,045 (66)†
No new drugs	242 (5)	180 (6)

Abbreviations: ASCT, autologous stem-cell transplantation; HR-CA, high-risk chromosomal abnormalities [defined by the presence of del(17p), translocation t(4;14), or translocation t(14;16)]; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase.
*Seven hundred twenty-two patients received immunomodulatory agents and proteasome inhibitors and were counted twice.
†Five hundred ten patients received immunomodulatory agents and proteasome inhibitors and were counted twice.

Table 3. ISS, CA, and LDH Distribution in Patients Included in R-ISS Analysis (n = 3,060)

	No. of Patients (%)		
	ISS Stage I (n = 1,171)	ISS Stage II (n = 1,174)	ISS Stage III (n = 715)
No other risk factors	863 (74)	763 (65)	406 (57)
Plus high-risk CA	200 (17)	262 (22)	159 (22)
Plus high LDH level	84 (7)	114 (10)	107 (15)
Plus high-risk CA and high LDH level	24 (2)	35 (3)	43 (6)

Abbreviations: ISS: International Staging System, CA: chromosomal abnormalities, LDH: lactate dehydrogenase; R-ISS, revised International Staging System.

with ISS stage III, 57% had standard-risk CA and normal LDH levels (Table 3).

Individual ISS, CA, and LDH

The individual role of each predictor was initially evaluated in the total population of 4,445 patients. One thousand six hundred fifteen patients (36%) had ISS stage I, 1,630 (37%) had ISS stage II, and 987 (22%) had ISS stage III; 213 patients (5%) had missing data. At a median follow-up of 46 months, the 5-year OS rate was 77% for ISS stage I, 62% for ISS stage II, and 47% for ISS stage III ($P < .001$); the 5-year PFS rate was 49% for ISS stage I, 36% for ISS stage II, and 30% for ISS stage III ($P < .001$).

Two thousand seven hundred eighteen patients (61%) had standard-risk CA, 851 patients (19%) had high-risk CA, and 876 patients (20%) had missing data. The 5-year OS rate was 69% in the standard-risk group and 50% in the high-risk group ($P < .001$), whereas the 5-year PFS rates were 45% and 24% ($P < .001$), respectively.

Three thousand four hundred forty-three patients (77%) had a normal LDH level, 530 patients (12%) had a high LDH level, and 472 patients (11%) had missing data. The 5-year OS rate was 68% for patients with normal LDH and 47% for patients with high LDH ($P < .001$), whereas the 5-year PFS rates were 42% and 31% ($P = .004$), respectively.

Combined ISS, CA, and LDH

The K-adaptive partitioning was performed in 3,060 patients with ISS, CA, and LDH data. The following three ISS/CA/LDH groups were identified (Table 1): 871 patients (28%) with R-ISS stage I, (ISS stage I, no high-risk CA, and normal LDH); 295 patients (10%) with R-ISS stage III (ISS stage III plus high-risk CA or high LDH); and 1,894 patients (62%) with R-ISS stage II (all the other ISS/CA/LDH combinations).

At a median follow-up of 46 months, the 5-year OS was 82% for R-ISS stage I, 62% for R-ISS stage II, and 40% for R-ISS stage III, with a median OS time of not reached for R-ISS stage I, 83 months for R-ISS stage II, and 43 months for R-ISS stage III (Fig 1). The 5-year PFS rate was 55% for R-ISS stage I, 36% for R-ISS stage II, and 24% for R-ISS stage III, with a median PFS time of 66 months for R-ISS stage I, 42 months for R-ISS stage II, and 29 months for R-ISS stage III (Fig 2).

In the univariable Cox analysis, the risk of death was increased for ISS stage II versus I (hazard ratio [HR], 2.39) and stage III versus I (HR, 4.68). Similarly, the risk of death was higher for high-risk CA

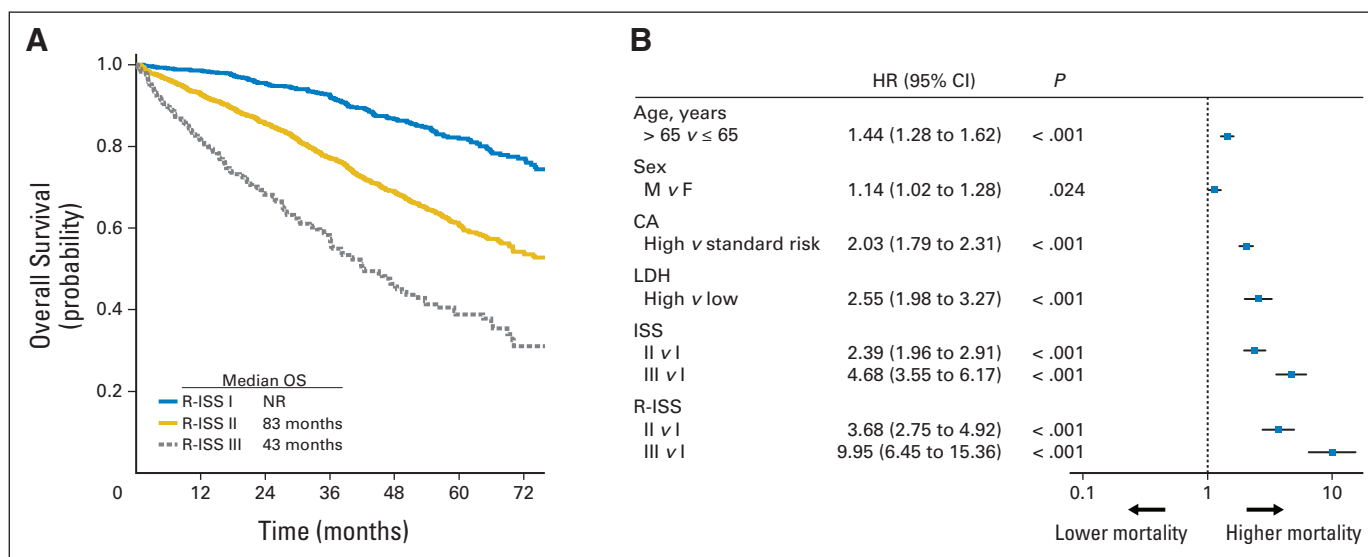


Fig 1. (A) Overall survival (OS) in patients with multiple myeloma stratified by revised International Staging System (R-ISS) algorithm. Median OS was not reached for patients included in R-ISS stage I, whereas it was 83 months for R-ISS stage II and 43 months for R-ISS stage III. (B) Univariable analysis of OS. CA, chromosomal abnormalities; F, female; HR, hazard ratio; LDH, lactate dehydrogenase; M, male; NR, not reached.

versus standard-risk CA (HR, 2.03), as well as for high LDH versus normal LDH (HR, 2.55). By applying the R-ISS, the mortality risk was considerably increased for R-ISS stage II versus I (HR, 3.68), as well as for R-ISS stage III versus I (HR, 9.95; Fig 1). The risk of progression was higher for ISS stage II versus I (HR, 1.64) and stage III versus I (HR, 2.18). Similarly, the risk of progression was increased for high-risk CA versus standard-risk CA (HR, 1.82), as well as for high LDH versus normal LDH (HR, 1.34). The risk of progression was higher for R-ISS stage II versus I (HR, 2.09), as well as for R-ISS stage III versus I (HR, 3.58; Fig 2).

In the multivariable Cox model for OS, including age, sex, and R-ISS, the risk of death was increased for age more than 65 years (HR,

1.32; 95% CI, 1.14 to 1.52; $P < .001$), male sex (HR, 1.16; 95% CI, 1.02 to 1.33; $P = .029$), R-ISS stage II versus I (HR, 3.59; 95% CI, 2.68 to 4.80; $P < .001$), and R-ISS stage III versus I (HR, 9.64; 95% CI, 6.24 to 14.88; $P < .001$). In the multivariable Cox model for PFS, the risk of progression was higher for age greater than 65 years (HR, 1.57; 95% CI, 1.42 to 1.75; $P < .001$), R-ISS stage II versus I (HR, 1.99; 95% CI, 1.61 to 2.37; $P < .001$), and R-ISS stage III versus I (HR, 3.37; 95% CI, 2.54 to 4.56; $P < .001$).

Subgroup analyses for PFS and OS were also performed. The R-ISS staging system confirms its prognostic role in patients younger and older than 65 years of age (Appendix Fig A1, online only) as well as in patients who did and who did not receive ASCT, PIs, and IMiDs (Fig 3).

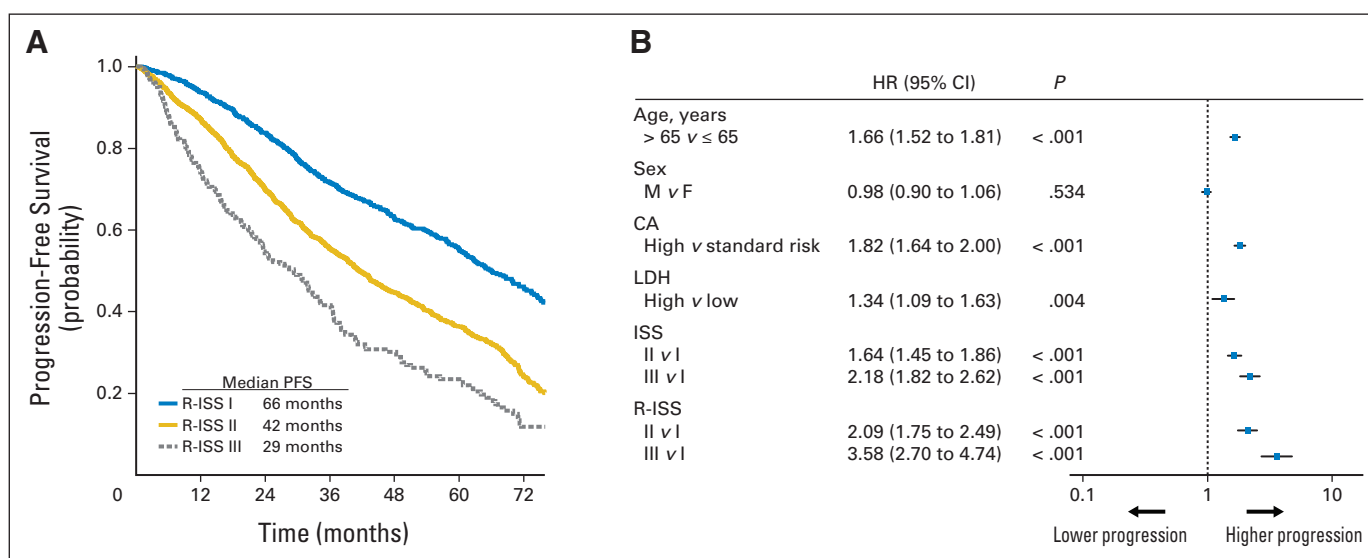


Fig 2. (A) Progression-free survival (PFS) in patients with multiple myeloma stratified by revised International Staging System (R-ISS) algorithm. Median PFS was 66 months for patients with R-ISS stage I, 42 months for patients with R-ISS stage II, and 29 months for patients with R-ISS stage III. (B) Univariable analysis of PFS. CA, chromosomal abnormalities; F, female; HR, hazard ratio; LDH, lactate dehydrogenase; M, male; NR, not reached.

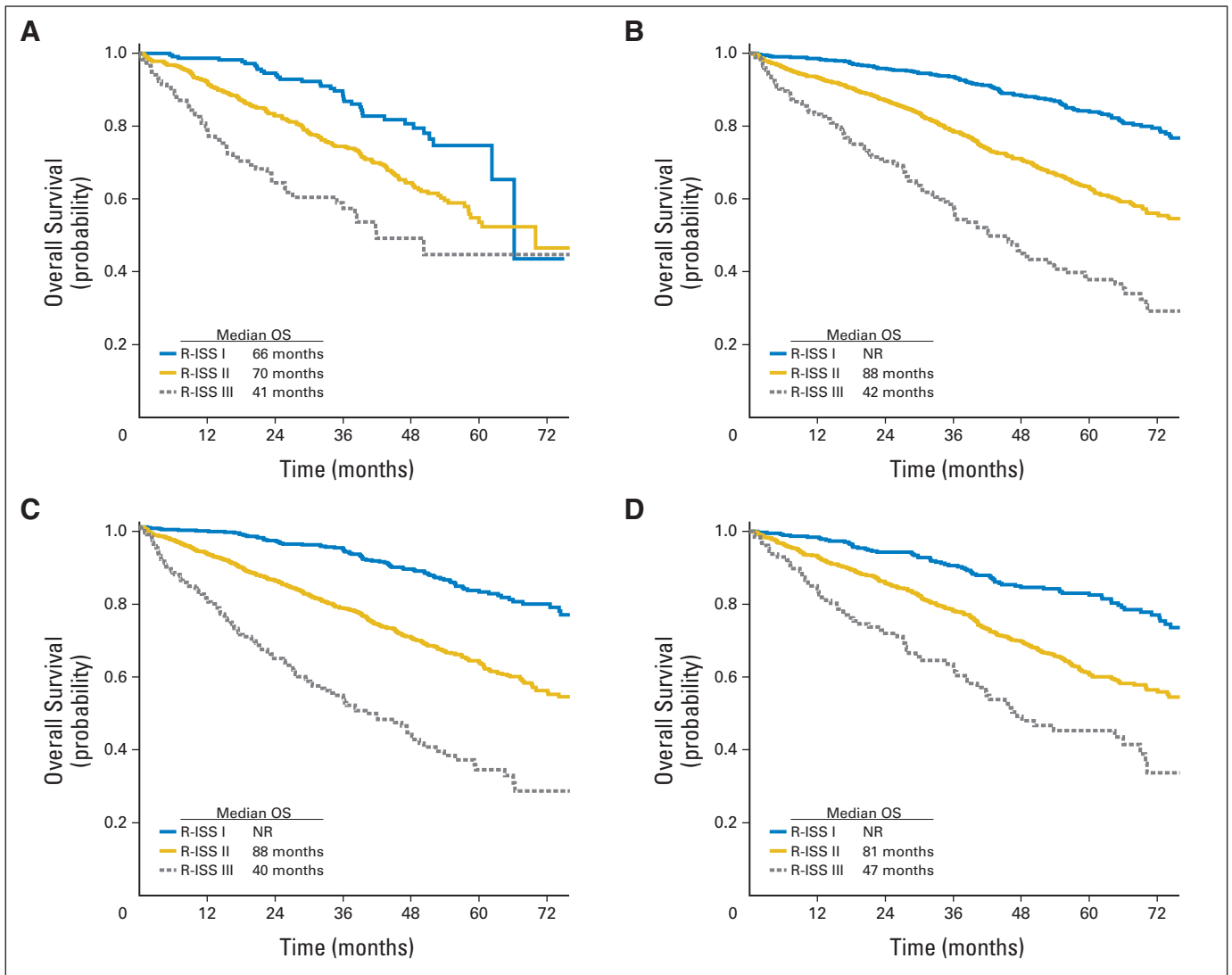


Fig 3. Revised International Staging System (R-ISS) and overall survival (OS) by type of treatment. (A) OS in regimens non-transplantation-based regimens. (B) OS in transplantation-based regimens. (C) OS in immunomodulatory-based regimens. (D) OS in proteasome inhibitor-based regimens. NR, not reached.

DISCUSSION

In this study, the most common prognostic tools (ISS stage, CA, and serum LDH level) were combined to define a simple, reliable, and pragmatic risk stratification of patients with NDMM. The R-ISS allowed a clear identification of the following three survival patterns through a simplified rule: R-ISS stage I includes ISS stage I, no high-risk CA, and normal LDH; R-ISS stage III includes ISS stage III with high-risk CA and/or high LDH levels; R-ISS stage II includes all the remaining conditions. Patients with R-ISS stage I, II, and III had 5-year OS rates of 82%, 62%, and 40%, respectively.

We initially evaluated the prognostic power of each single component of the R-ISS. The impact of ISS was confirmed for both OS (ISS stage III ν I: HR, 4.68) and PFS (ISS stage III ν I: HR, 2.18). As for CA, the presence of del(17p), translocation t(4;14), or translocation t(14;16) commonly identifies high-risk patients with poor outcome,^{3,4} and our study confirmed their prognostic impact for both OS (HR, 2.03) and PFS (HR, 1.82). Consistent with previous

studies, we found that high serum LDH level predicted worse OS (HR, 2.55) and PFS (HR, 1.34).

Subsequently, we developed the R-ISS algorithm that combines these three prognostic features. Our major aim was to create a simple and easily applicable model that combined validated and reliable disease-related prognostic factors. The combination of three different prognostic tools in the R-ISS allows a better evaluation of patient prognosis; approximately 26% of patients would have been wrongly allocated to a good-prognosis group if we had considered only one of these three factors.

In the univariable Cox analyses, we found that ISS stage III, high-risk CA, and elevated serum LDH were associated with a significantly poorer OS (HR from 2.03 to 4.68). Their combination in the R-ISS improved the stratification and the impact on OS (HR from 3.68 to 9.95). The prognostic impact of R-ISS on OS was confirmed independently of age and therapy.

To define the three R-ISS stages, we did not use the classical recursive partitioning, which is a multivariable statistical method

based on a binary tree representation, because it can easily manage categorical but not continuous variables.²⁶ Conversely, we adopted K-partitioning, a new technique that can manage censored survival data. K-partitioning provides minimal-based partitioning rules by log-rank test and finds an optimal set of cutoff points, and the number of groups does not need to be established in advance.²⁵

Previous studies have combined different prognostic tools (Appendix Table A1).¹⁰⁻¹³ Compared with other studies, the R-ISS has been developed in a larger sample size of 3,060 patients, including both young and elderly patients. In the other studies, the majority of patients were in the low-risk group (42% to 58%)¹⁰⁻¹³; in our analysis, 62% of patients were in the intermediate-risk group, whereas 28% were in the low-risk group and 10% were in the high-risk group. This distribution may explain the slightly better survival dissection among the different groups in our study, with HR for OS ranging from 3.68 to 9.95. We based our staging system on validated, simple, easily applicable, and reliable disease-related prognostic factors. There are novel, alternative approaches, such as gene expression profiling and single nucleotide polymorphisms, currently used for a detailed molecular analysis of MM. Yet, studies including gene expression profiling and single nucleotide polymorphism analyses showed inconsistent results, and further validation to achieve a more general consensus is still necessary.²⁷⁻²⁹ In addition, these techniques are quite complex and expensive, which limits their routine use.

In our study, 95% of patients received novel agents. Although this was not the objective of our analysis, our results showed an improvement in OS with novel therapies across prognostic subgroups. In the original ISS study including patients worldwide treated from 1981 to 2002, with minimal exposure to any novel agents, the median OS was 62 months for patients with ISS stage I, 44 months for patients with ISS stage II, and 29 months for patients with ISS stage III. In our analysis, the median OS was not reached for patients with ISS stage I, 87 months for patients with ISS stage II, and 56 months in patients ISS stage III.²

Our study has some limitations. We included only patients enrolled onto experimental trials (65% < 65 years old). We excluded some patients from the final analysis as a result of the lack of baseline data; in addition, information about chromosome 1 abnormalities was not collected in all trials, and thus we could not include this prognostic parameter. There was no interlaboratory standardization of FISH analysis, and heterogeneous cutoff levels for LDH were used in the different trials. In our model, we did not include host-related prognostic factors such as age, performance status, and comorbidities, which still play an important role in defining patient prognosis. The relatively short median follow-up time is another limitation. Furthermore, we used a single-step modeling

approach, without splitting the series into training and validation autonomous sets. The lack of a real validation sample can be a limitation of the analysis. Nevertheless, both the large sample size and the homogeneity of the main clinical characteristics were expected to minimize the risk of data overfitting.

Future analyses will try to overcome such limitations and will validate this new risk stratification in population-based studies, including a higher proportion of elderly patients. The European Myeloma Network will also focus on FISH standardization in MM, and future efforts will be directed to combine both disease-related and patient-related factors to develop a more comprehensive prognostic evaluation.

In conclusion, there is a clear need for a better differentiation of patients with MM. MM can no longer be considered a single disease, but a mix of different disease entities. Today, new treatments are available, and survival of patients with MM has significantly improved. In clinical practice, a better definition of MM subgroups is essential to provide more effective personalized therapies. The R-ISS staging system is a new risk stratification algorithm with an improved prognostic power compared with the individual ISS, CA, and LDH parameters. It includes simple, reliable, and widely used prognostic markers, and it allows the identification of three different MM entities with clearly different outcomes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Final approval of manuscript: All authors

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Appendix

Fluorescent in situ hybridization analyses were performed in a few European laboratories. Despite interlaboratory variability, all the analyses were performed on purified plasma cells obtained with immunomagnetic techniques, and the analyses of p53 deletion, t(4,14), and t(14;16) were commonly included in each multiple myeloma panel and tested using commercial probes. Of note, however, the cutoff levels were not identical, ranging from 8% to 20% for numerical aberrations and from 10% to 15% for immunoglobulin H translocations.

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Table A1. Previous Studies Assessing Combinations of Prognostic Tools

Risk Category	OS Rate (%)
ISS+CA ¹⁰ in ASCT-eligible patients with NDMM	
Favorable ISS stage I and no t(4;14) or del(17p13)	72 at 60 months
Intermediate, not favorable or poor categories	62 at 60 months
Poor ISS stage II/III and t(4;14) or del(17p13)	41 at 60 months
ISS+CA ¹¹ in ASCT-eligible and -ineligible patients with NDMM	
Favorable ISS stage I/II and no t(4;14), t(14;16), +1q21, del(13), or del(17)	50 at 68 months
Intermediate ISS stage I and > 1 CA, or ISS stage II and 1 CA, or ISS stage III and ≤ 1 CA	50 at 41 months
Ultra-high-risk ISS stage II/III and > 1 CA	50 at 19 months
ISS+CA ¹² in ASCT-eligible and -ineligible patients with NDMM	
Favorable ISS stage I/II and no t(4;14) or del(17)	71 at 48 months
Intermediate ISS stage III and no t(4;14) or del(17), or ISS stage I and t(4;14) or del(17)	45 at 48 months
Poor ISS stage II/III and t(4;14) or del(17p)	33 at 48 months
ISS+CA+LDH ¹³ in ASCT-eligible patients with NDMM	
Score 0, no adverse factors of the other categories	93 at 24 months
Score 1, only 1 adverse factor of categories 2 and 3	85 at 24 months
Score 2, high LDH, ISS stage III, no t(4;14) or del(17p)	67 at 24 months
Score 3, t(4;14) and/or del(17p), and ISS stage III and/or high LDH	55 at 24 months

Abbreviations: ASCT, autologous stem-cell transplantation; CA, chromosomal abnormalities; ISS, International Staging System; LDH, lactate dehydrogenase; NDMM, newly diagnosed multiple myeloma; OS, overall survival.

Table A2. Patient Demographic and Clinical Characteristics in the 11 Studies Included in the Analysis

Characteristic	No. of Patients (%)										
	IST-CAR-506 ¹⁴	EMN 01 ¹⁵	MM-EMN-441 ¹⁶	MM-RV-PI-209 ¹⁷	GIMEMA-MM-05-05 ¹⁸	GIMEMA-MM-03-05 ¹⁹	MMY2069 ²⁰	HOVON-65/GMMG-HD4 ²¹	VTD v TD ²²	GEM05MENOS65 ²³	IFM 2005-01 ²⁴
Sex											
Male	27 (47)	322 (49)	196 (50)	219 (54)	53 (52)	252 (49)	78 (51)	500 (60)	273 (57)	207 (53)	266 (55)
Female	31 (53)	338 (51)	193 (50)	183 (46)	49 (48)	259 (51)	74 (49)	327 (40)	201 (42)	179 (47)	216 (45)
Missing	—	2	—	—	—	—	—	—	—	—	—
CA by iFISH											
del(17)	8 (14)	7 (11)	29 (7)	42 (14)	12 (15)	55 (11)	19 (12)	65 (8)	33 (7)	19 (5)	46 (9)
t(4;14)	9 (16)	63 (9)	41 (10)	42 (14)	16 (20)	59 (11)	9 (6)	70 (8)	87 (18)	42 (10)	30 (6)
t(14;16)	1 (2)	16 (2)	19 (5)	14 (3)	4 (6)	15 (3)	5 (3)	NA	NA	10 (2)	NA
Missing	7 (12)	129 (19)	150 (38)	111 (27)	28 (27)	135 (26)	25 (16)	166 (20)	33 (7)	62 (16)	16 (3)
ISS stage											
I	16 (27)	183 (28)	172 (44)	192 (48)	48 (47)	115 (23)	41 (27)	288 (35)	214 (45)	147 (38)	199 (41)
II	19 (33)	299 (45)	155 (40)	115 (29)	30 (29)	188 (37)	44 (29)	274 (33)	183 (38)	160 (42)	163 (34)
III	23 (40)	178 (27)	62 (16)	95 (23)	12 (12)	104 (20)	67 (44)	188 (23)	77 (16)	75 (20)	106 (22)
Missing	—	2	—	—	12 (12)	104 (20)	—	77 (9)	—	4	14 (3)
LDH level											
Normal	35 (61)	471 (71)	311 (80)	361 (90)	77 (75)	373 (73)	78 (51)	660 (80)	404 (85)	326 (84)	347 (72)
High	5 (8)	55 (8)	24 (6)	40 (10)	9 (9)	51 (10)	17 (11)	144 (17)	42 (9)	60 (16)	83 (17)
Missing	18 (31)	136 (21)	54 (14)	1	16 (16)	87 (17)	57 (38)	23 (3)	28 (6)	—	52 (11)

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; NA, not available; TD, thalidomide plus dexamethasone; VTD, bortezomib with thalidomide plus dexamethasone.

Table A3. Treatment Regimens in the Source Studies

Trial	Regimens and Doses	No. of Patients	Age (years)
IST-CAR-506 ¹⁴	C: carfilzomib IV 20 mg/m ² per day on days 1 and 2 of cycle 1 followed by 36 mg/m ² per day on days 8, 9, 15, and 16 and then for all subsequent cycles C: cyclophosphamide PO 300 mg/m ² per day on days 1, 8, and 15 D: dexamethasone PO 40 mg per day on days 1, 8, 15, and 22 (nine 28-days cycles followed by maintenance with carfilzomib alone until PD)	58	≥ 65
EMN 01 ¹⁵			
Arm A	R: lenalidomide PO 25 mg per day for 21 days D: dexamethasone PO 40 mg per day on days 1, 8, 15, and 22 or 20 mg in patients > 75 years old	222	≥ 65
Arm B	M: melphalan PO 0.18 mg/kg or 0.13 mg/kg in patients > 75 years old on days 1-4 P: prednisone PO 1.5 mg/kg per day on days 1-4 R: lenalidomide PO 10 mg per day for 21 days	218	
Arm C	C: cyclophosphamide PO 50 mg per day for 21 days or 50 mg every other day in patients > 75 years old P: prednisone PO 25 mg every other day R: lenalidomide PO 25 mg per day for 21 days (nine 28-day cycles followed by maintenance with lenalidomide or lenalidomide and prednisone)	222	
RV-MM-EMN-441 ¹⁶			
Arm A	C: cyclophosphamide PO 300 mg/m ² per day on days 1, 8, and 15 R: lenalidomide PO 25 mg per day for 21 days D: dexamethasone PO 40 mg per day on days 1, 8, 15, and 22 (six 28-day cycles followed by maintenance with lenalidomide or lenalidomide and prednisone)	194	≤ 65
Arm B	2 doses of melphalan IV 200 mg/m ² followed by stem-cell support (followed by maintenance with lenalidomide or lenalidomide and prednisone)	195	
MM-RV-PI-209 ¹⁷			
Arm A	M: melphalan PO 0.18 mg/kg per day on days 1-4 P: prednisone PO 2 mg/kg per day on days 1-4 R: lenalidomide PO 10 mg per day for 21 days (six 28-days cycles followed by maintenance with lenalidomide or no maintenance)	202	
Arm B	2 doses of melphalan IV 200 mg/m ² followed by stem-cell support (followed by maintenance with lenalidomide or no maintenance)	200	≤ 65
GIMEMA-MM-05-05 ¹⁸	P: bortezomib IV 1.3 mg per day on days 1, 4, 8, and 11 A: pegylated liposomal doxorubicin IV 30 mg/m ² on day 4 D: dexamethasone on days 1-4, 8-11, and 15-18 in cycle 1 and on days 1-4 in cycles 2-4 2 doses of melphalan IV 100 mg/m ² followed by consolidation with lenalidomide 25 mg per day for 21 days + prednisone 50 mg every other day followed by maintenance with lenalidomide 10 mg per day for 21 days until PD	102	≤ 75
GIMEMA-MM-03-05 ¹⁹			
Arm A	V: bortezomib IV 1.3 mg per day on days 1, 8, 15, and 22 M: melphalan PO 9 mg/m ² per day on days 1-4 or 2 mg every other day P: prednisone PO 60 mg/m ² per day on days 1-4	257	≥ 65
Arm B	V: bortezomib IV 1.3 mg/m ² per day on days 1, 8, 15, and 22 M: melphalan PO 9 mg/m ² per day on days 1-4 P: prednisone os 60 mg/m ² per day on days 1-4 T: thalidomide PO 50 mg (only in VMPT arm, nine 28-day cycles followed by maintenance with bortezomib and thalidomide until PD)	254	
MMY2069 ²⁰			
Group 1	V: bortezomib SC 1.3 mg/m ² per day on days 1, 8, 15, and 22 P: prednisone PO 50 mg every other day	51	
Group 2	C: cyclophosphamide PO 50 mg every other day V: bortezomib SC 1.3 mg/m ² per day on days 1, 8, 15, and 22 P: prednisone PO 50 mg every other day	51	
Group 3	V: bortezomib SC 1.3 mg per day on days 1, 8, 15, and 22 M: melphalan PO 2 mg every other day P: prednisone PO 50 mg every other day (nine 28-days cycles followed by maintenance with bortezomib until PD)	50	
HOVON-65/GMMG-HD4 ²¹			
Arm A	P: bortezomib IV 1.3 mg per day on days 1, 4, 8, and 11 A: doxorubicin IV 9 mg/m ² per day on days 1-4 D: dexamethasone PO 50 mg per day on days 1-4, 9-12, and 17-20 (three 28-day cycles, followed by one or two doses of melphalan 200 mg/m ² and stem-cell support, followed by maintenance with IV bortezomib 1.3 mg/m ² once every 2 weeks for 2 years)	413	≤ 65
Arm B	V: vincristine IV 0.4 mg d 1-4 A: doxorubicin IV 9 mg/mq d 1-4 D: dexamethasone os 50 mg d 1-4, 9-12, 17-20 (three 28-day cycles followed by one or two doses of melphalan 200 mg/m ² and stem-cell support, followed by maintenance with thalidomide 50 mg per day for 2 years)	414	

continued on following page

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Table A3. Treatment Regimens in the Source Studies (continued)

Trial	Regimens and Doses	No. of Patients	Age (years)
VTD v TD ²²			
Arm A	V: bortezomib IV 1.3 mg per day on days 1, 4, 8, and 11 T: thalidomide PO 100 mg daily for the first 14 days and 200 mg daily thereafter D: dexamethasone PO 40 mg per day on days 1, 2, 4, 5, 8, 9, 11, and 12 (three 21-day cycles, followed by two doses of melphalan IV 200 mg/m ² and stem-cell support, followed by consolidation with two cycles of VTD)	236	≤ 65
Arm B	T: thalidomide PO 100 mg daily for the first 14 days and 200 mg daily thereafter D: dexamethasone PO 40 mg per day on days 1, 2, 4, 5, 8, 9, 11, and 12 (three 21-day cycles, followed by two doses of melphalan 200 mg/m ² and stem-cell support, followed by consolidation with two cycles of TD)	238	
GEM05MENOS65 ^{23*}			
Arm A	V: vincristine IV 0.03 mg/kg (upper limit, 2 mg) on day 1 B: carmustine 0.5 mg/kg IV on day 1 M: melphalan 0.25 mg/kg PO per day on days 1-4 C: cyclophosphamide 10 mg/kg IV on day 1 P: prednisone 1 mg/kg per day on days 1-4, 0.5 mg/kg per day on days 5-8, and 0.25 mg/kg per day on days 9-12 V: vincristine 1 mg IV on day 1 B: carmustine 30 mg/m ² IV on day 1 A: doxorubicin 40 mg/m ² IV on day 1 D: dexamethasone 40 mg PO per day on days 1-4, 9-12, and 17-20 (four 35-day alternating cycles followed by two bortezomib cycles on days 1, 4, 8, and 11, followed by one or two doses of melphalan 200 mg/m ² and stem-cell support)	129	≤ 65
Arm B	T: thalidomide PO 200 mg daily (with escalating doses from 50 to 100 to 200 mg) D: dexamethasone PO 40 mg per day on days 1-4 and 9-12 (six 4-week cycles, followed by one or two doses of melphalan 200 mg/m ² and stem-cell support)	127	
Arm C	V: bortezomib IV 1.3 mg/m ² per day on days 1, 4, 8, and 11 T: thalidomide PO 200 mg daily (with escalating doses from 50 to 100 to 200 mg) D: dexamethasone PO 40 mg per day on days 1-4 and 9-12 (six 4-week cycles, followed by one or two doses of melphalan 200 mg/m ² and stem cell support)	130	
IFM 2005-01 ²⁴			
Arm A1	V: vincristine 0.4 mg IV per day on days 1-4 (all cycles), 9-12, and 17-20 (cycles 1 and 2) A: doxorubicin 9 mg/m ² IV per day on days 1-4 (all cycles), 9-12, and 17-20 (cycles 1 and 2) D: dexamethasone 40 mg PO per day on days 1-4 (all cycles), 9-12, and 17-20 (cycles 1 and 2) (four 4-week cycles, followed by one or two doses of melphalan 200 mg/m ² and stem-cell support)	121	≤ 65
Arm A2	VAD (four 4-week cycles) plus: D: dexamethasone PO 40 mg per day on days 1-4 C: cyclophosphamide IV 400 mg/m ² on day 14 E: etoposide IV 40 mg/m ² per day on days 1-4 P: cisplatin IV 15 mg/m ² per day on days 1-4 (two 4-week cycles, followed by one or two doses of melphalan 200 mg/m ² and stem-cell support)	121	
Arm B1	V: bortezomib IV 1.3 mg/m ² per day on days 1, 4, 8, and 11 D: dexamethasone PO 40 mg per day on days 1-4 (all cycles), 9-12, and 17-20 (cycles 1 and 2) (four 3-week cycles, followed by one or two doses of melphalan 200 mg/m ² and stem-cell support)	121	
Arm B2	VD (four 3-week cycles) + DCEP (two 4-week cycles) followed by one or two doses of melphalan 200 mg/m ² and stem-cell support	119	
Abbreviations: IV, intravenous; PD, progression disease; PO, oral; SC, subcutaneous; TD, thalidomide plus dexamethasone; VTD, bortezomib with thalidomide plus dexamethasone.			
*Four patients, randomized in the study, were excluded from the analysis since they did not meet the eligibility criteria. ²⁰			

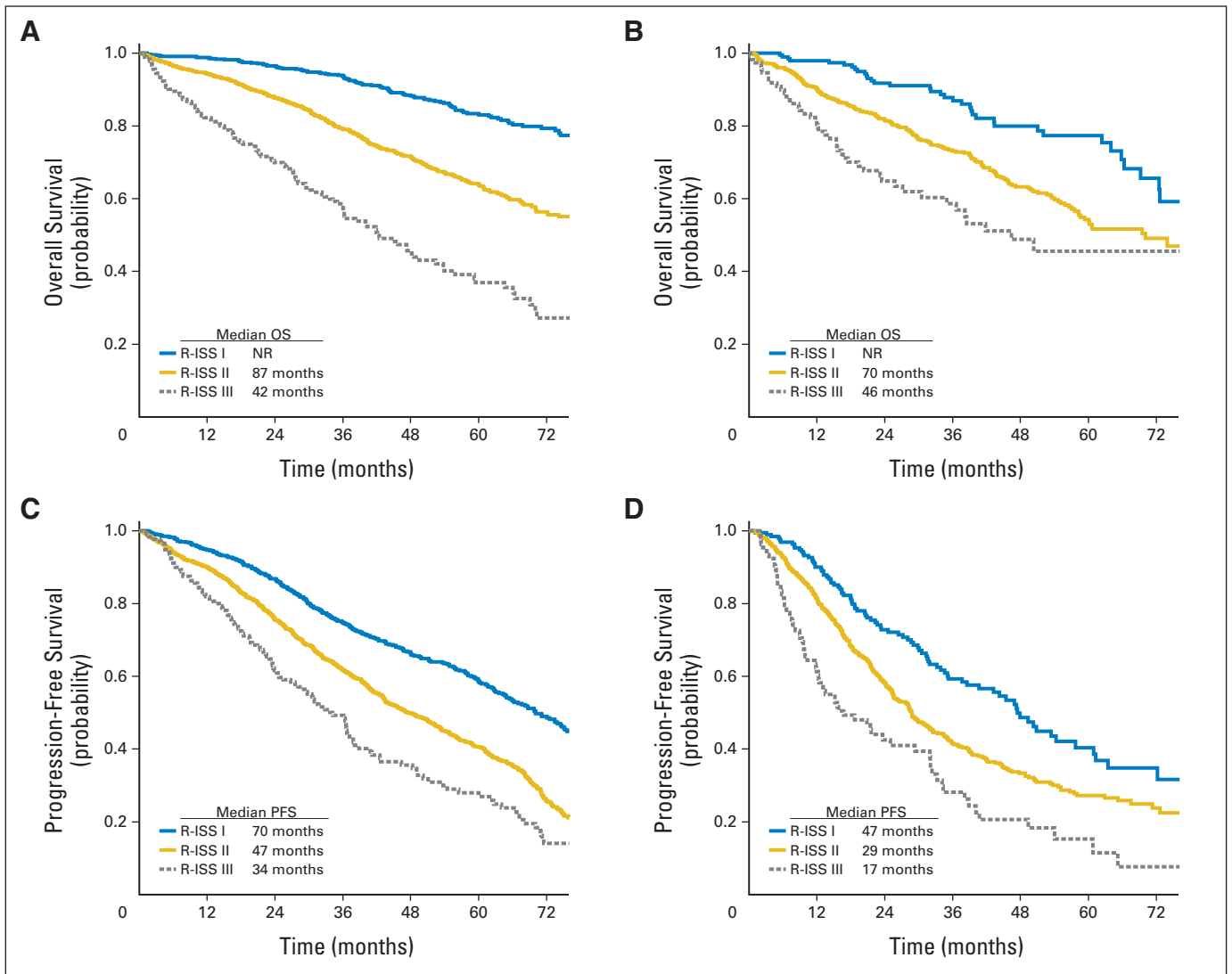


Fig A1. Revised International Staging System (R-ISS) and survival by age. (A) Overall survival (OS) in patients ≤ 65 years of age. (B) OS in patients older than age 65 years. (C) Progression-free survival (PFS) in patients ≤ 65 years old. (D) PFS in patients older than age 65 years. NR, not reached.