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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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)

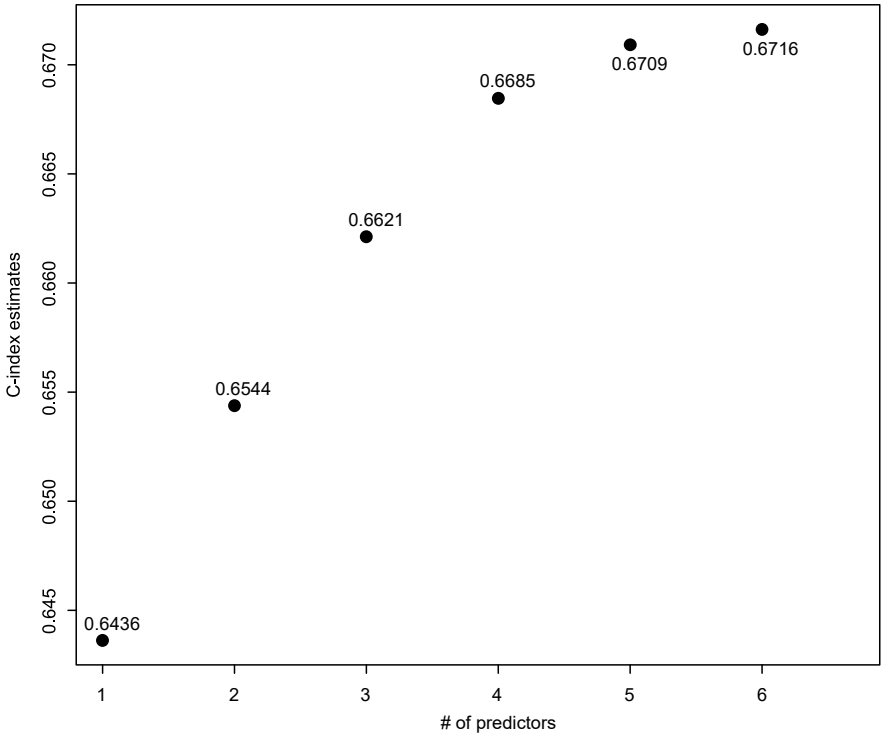
Prognostic score	R2-ISS low (I, n=428)	R2-ISS low-int (II, n=686)	R2-ISS int-high (III, n=917)	R2-ISS high (IV, n=195)
R-ISS I	428	169	0	0
R-ISS II	0	517	811	44
R-ISS III	0	0	106	151

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

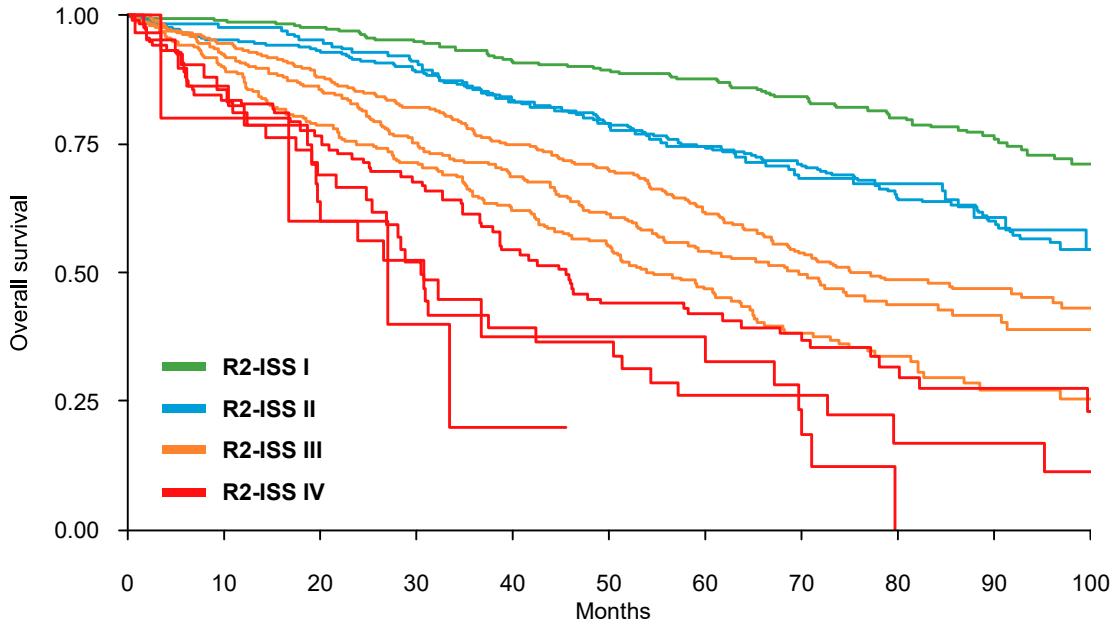
C-index estimates defined using the inverse probability of censoring weighted (IPCW) method at 60 months are shown.



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.

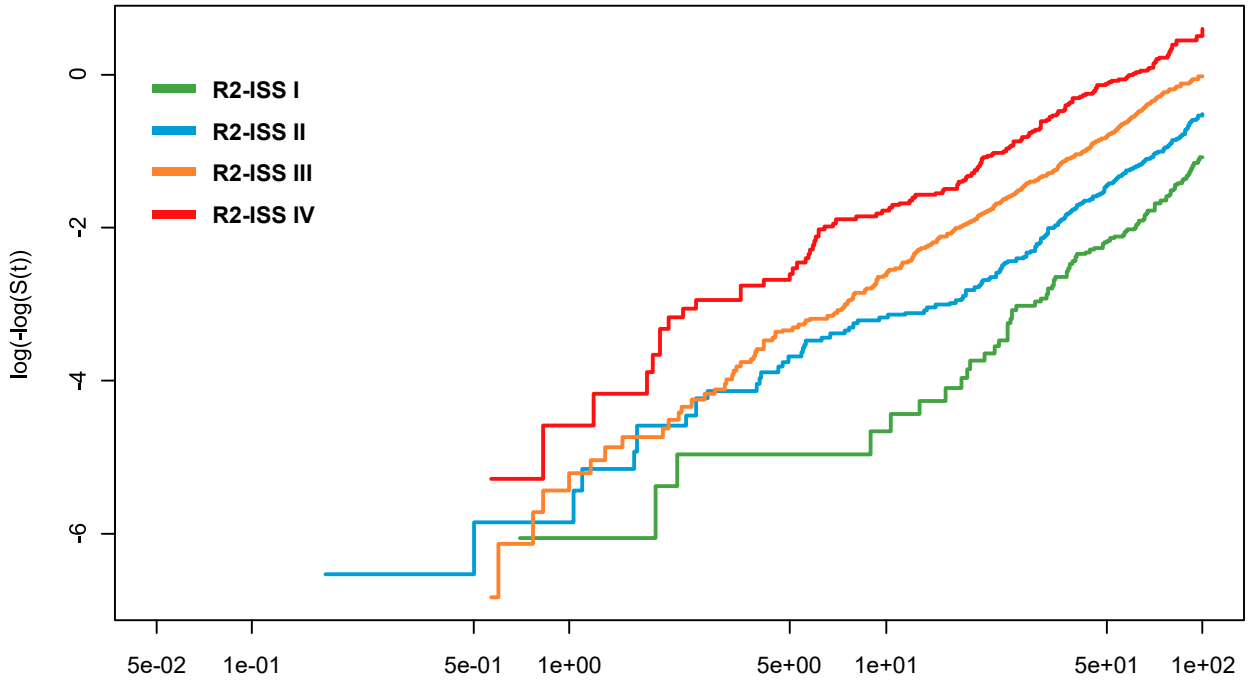


Abbreviations. OS, overall survival; R2-ISS, Second Revision of the International Staging System.

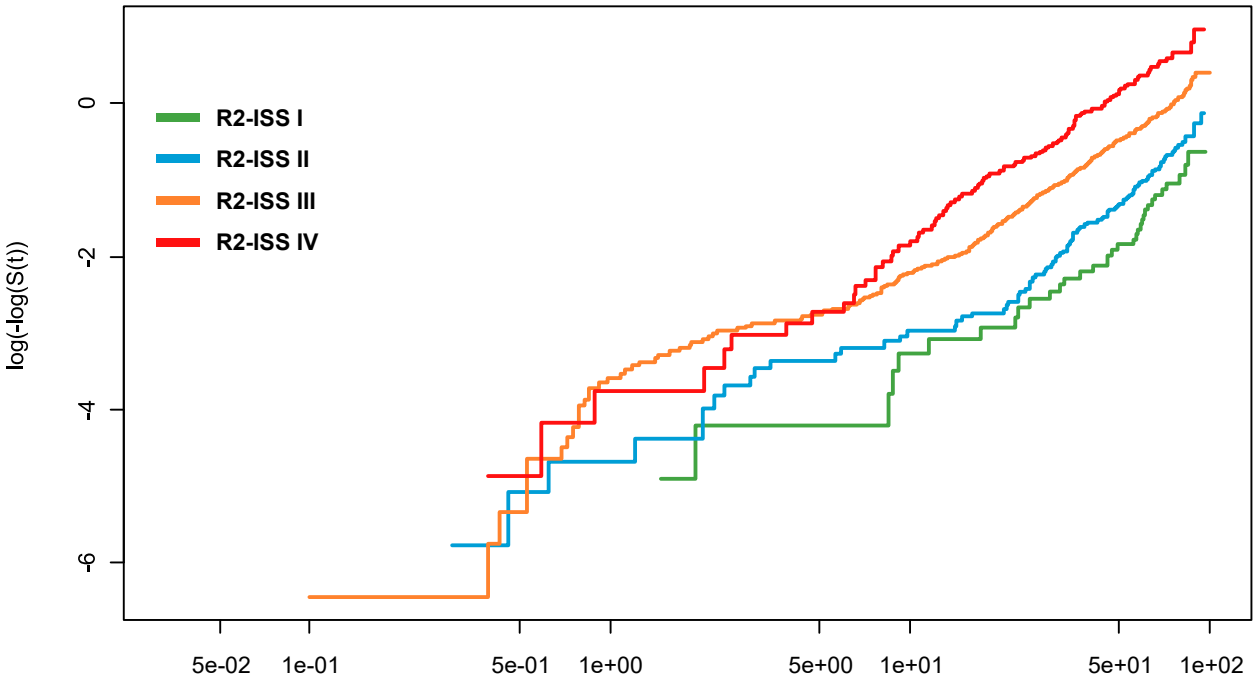
Figure S3. Proportional hazards assessment of the R2-ISS for OS

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

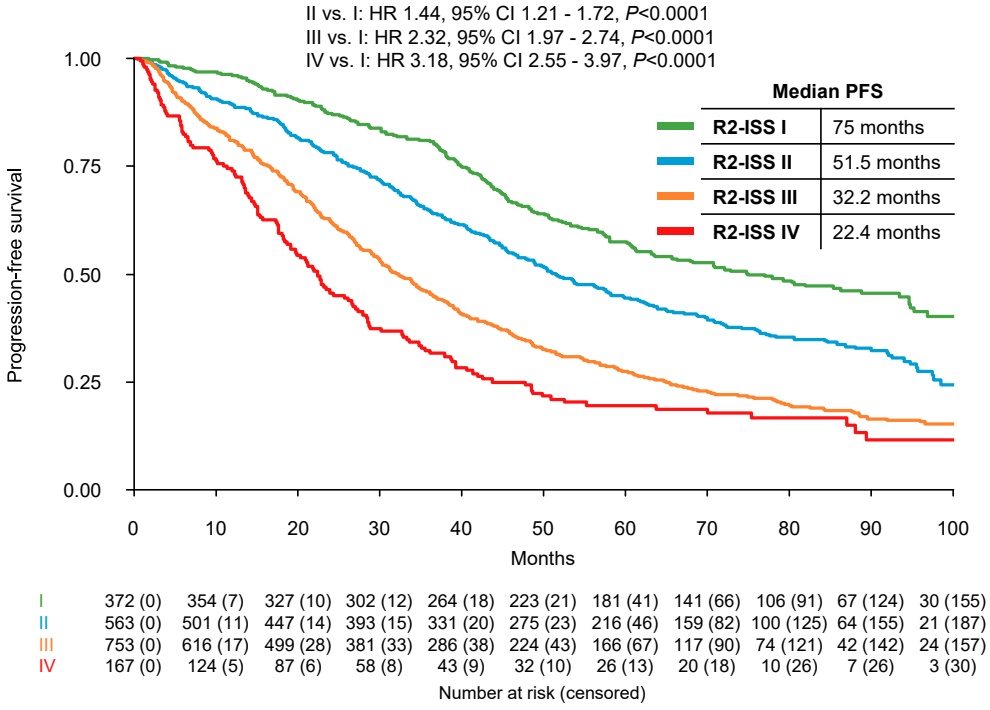


Abbreviations. R2-ISS, Second Revision of the International Staging System; OS, overall survival.

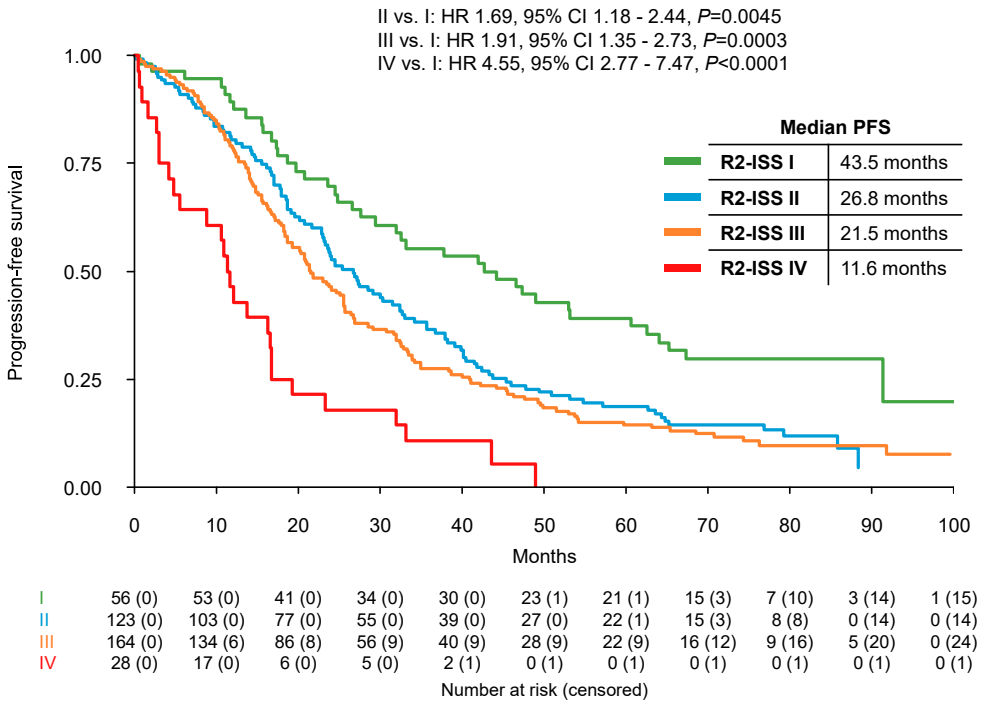
Figure S4. R2-ISS and PFS by transplant eligibility and type of treatment in the training set

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.

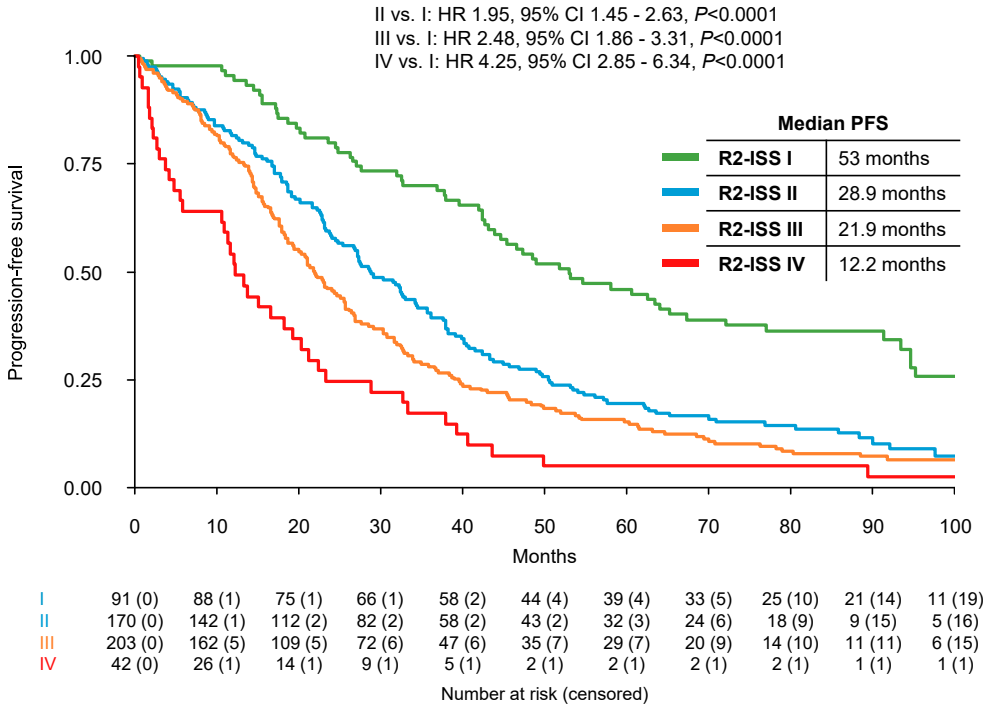
S4a. PFS in transplant-eligible patients



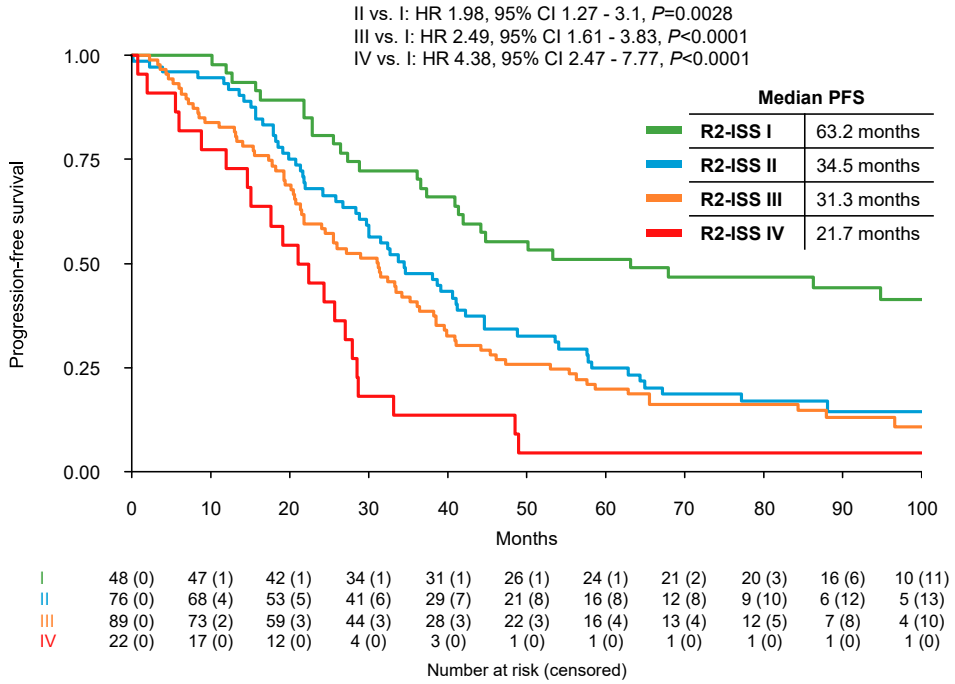
S4b. PFS in transplant-ineligible patients



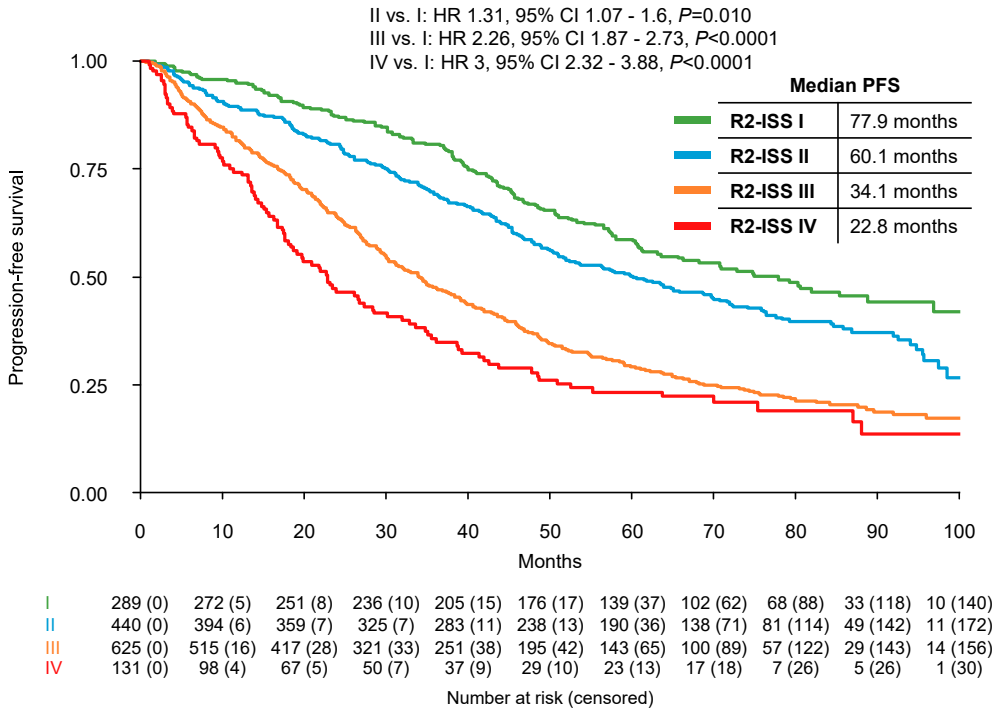
S4c. PFS in patients receiving IMiD-based regimens



S4d. PFS in patients receiving PI-based regimens



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

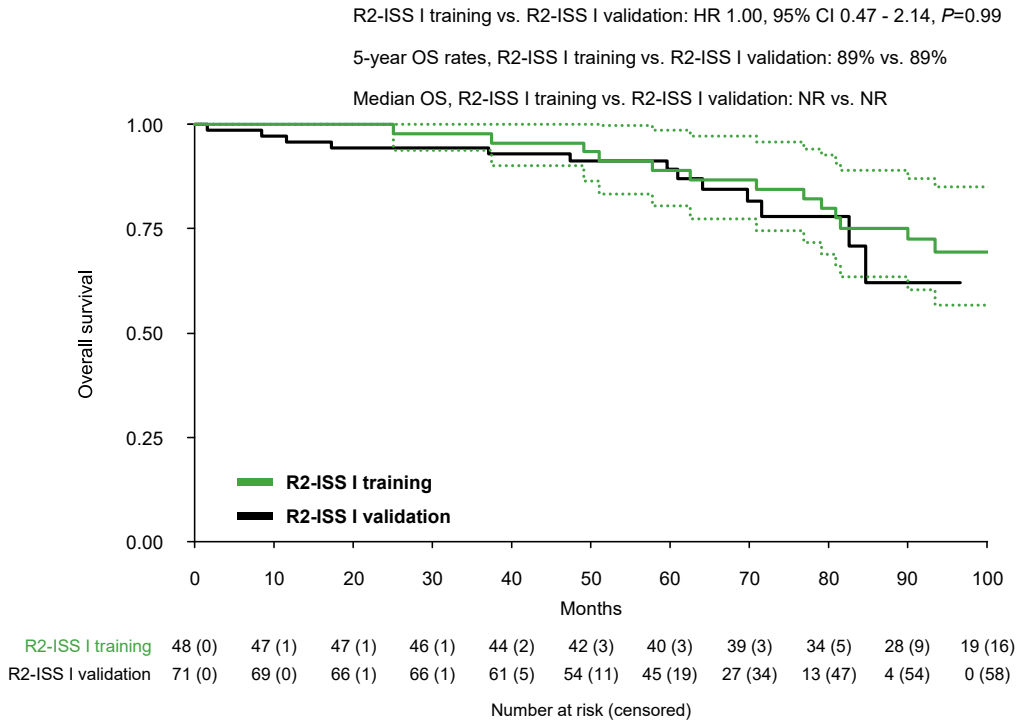


Abbreviations. R2-ISS, Second Revision of the International Staging System; PFS, progression-free survival; IMiDs, immunomodulatory drugs; PIs, proteasome inhibitors; HR, hazard ratio; CI, confidence interval; *P*, *P* value; NR, not reached.

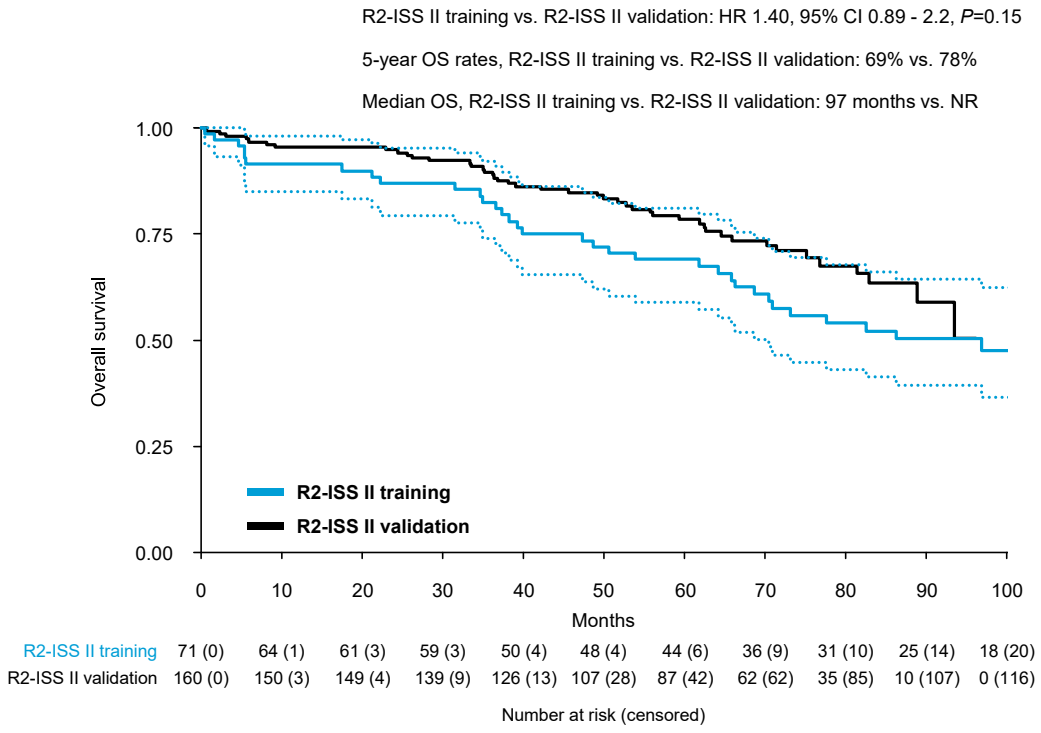
Figure S5. Calibration of the R2-ISS in transplant-eligible patients receiving an IMiD-based treatment

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.

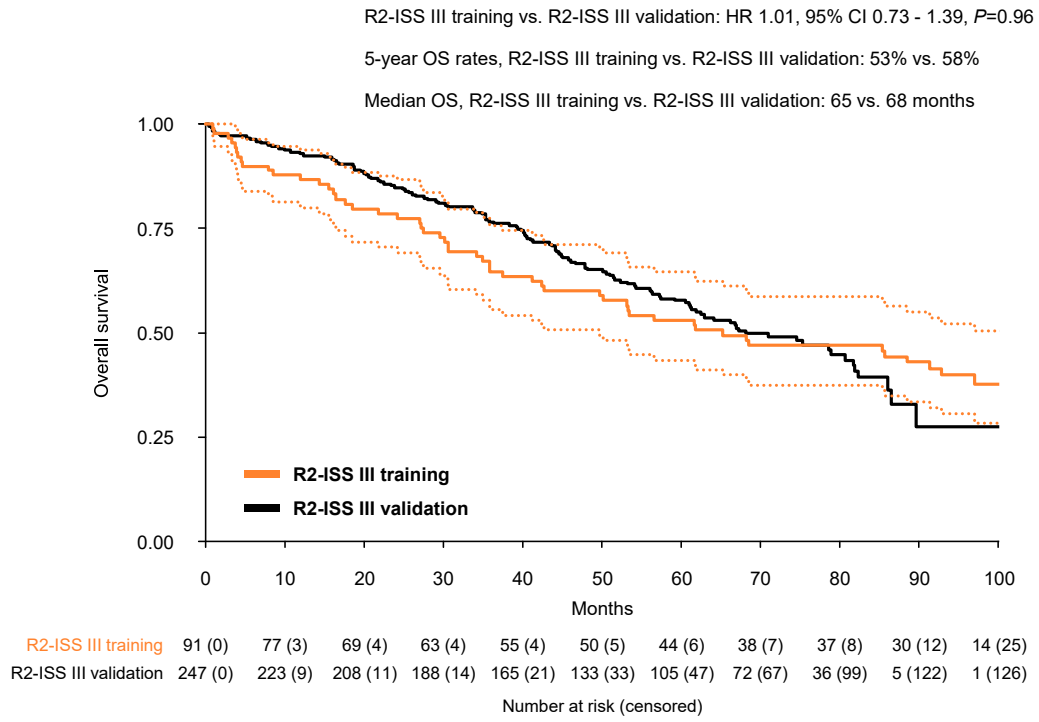
S5a. R2-ISS I



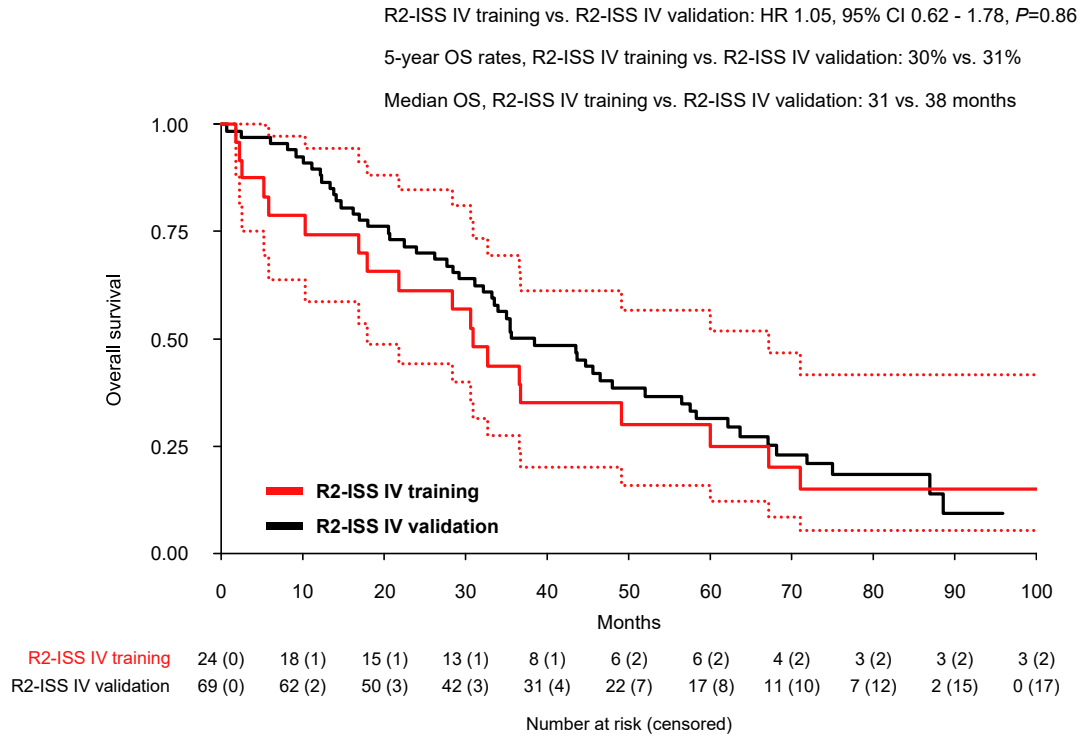
S5b. R2-ISS II



S5c. R2-ISS III



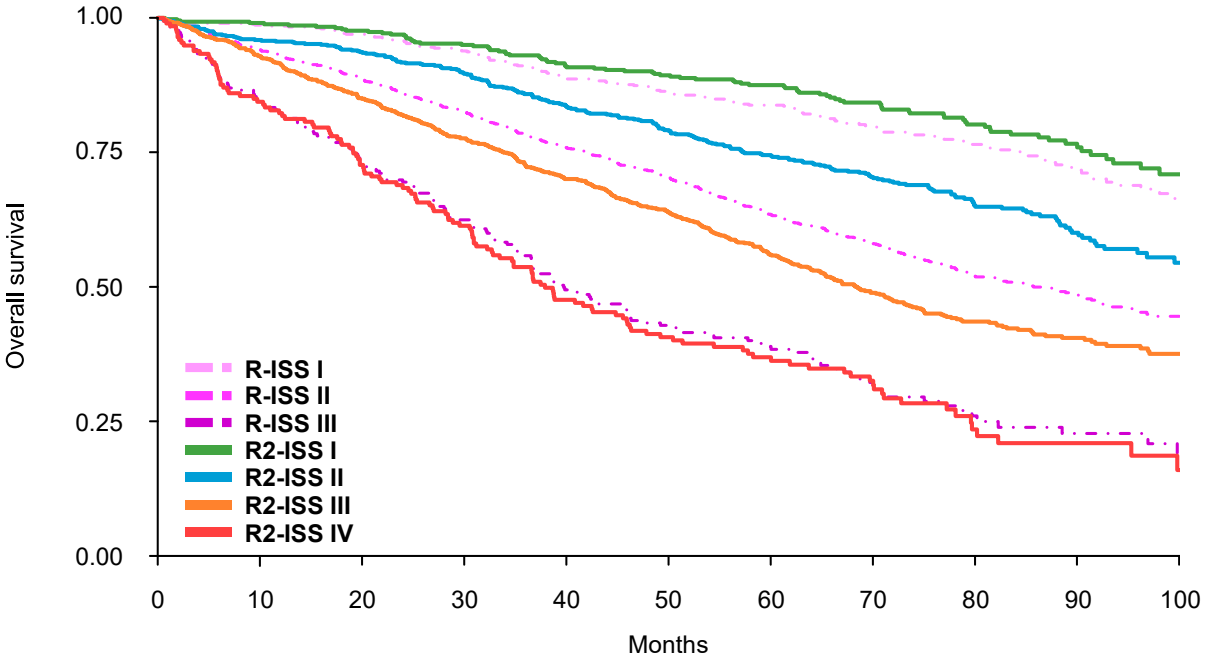
S5d. R2-ISS IV



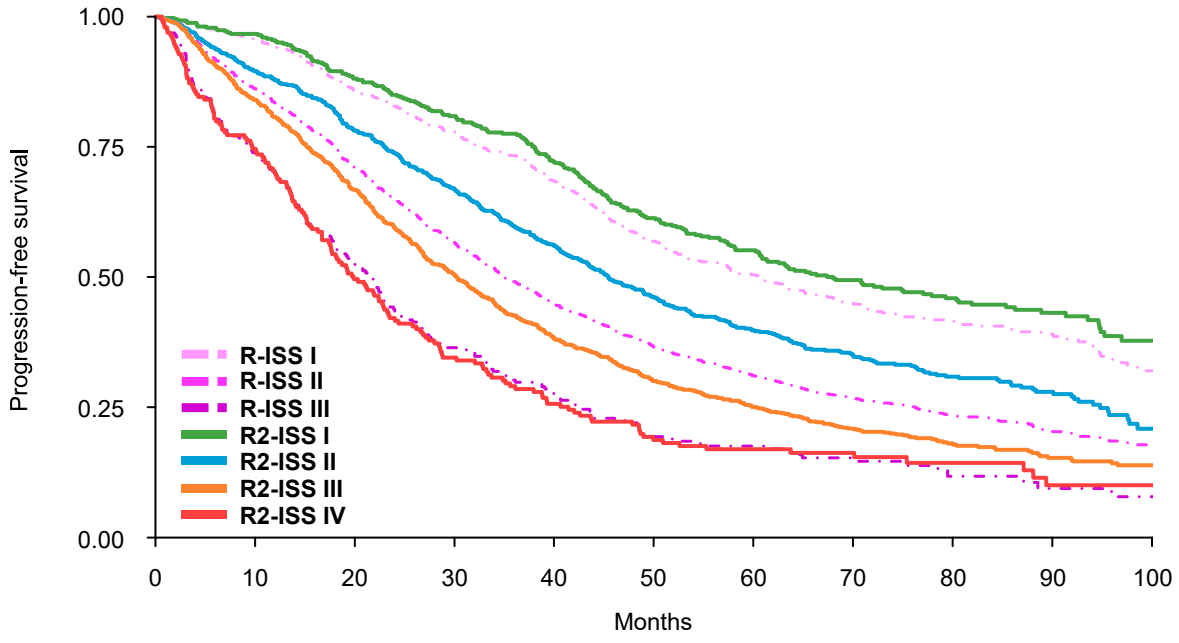
Abbreviations. R2-ISS, Second Revision of the International Staging System; IMiD, immunomodulatory drug; HR, hazard ratio; CI, confidence interval; *P*, *P* value; OS, overall survival; NR, not reached.

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

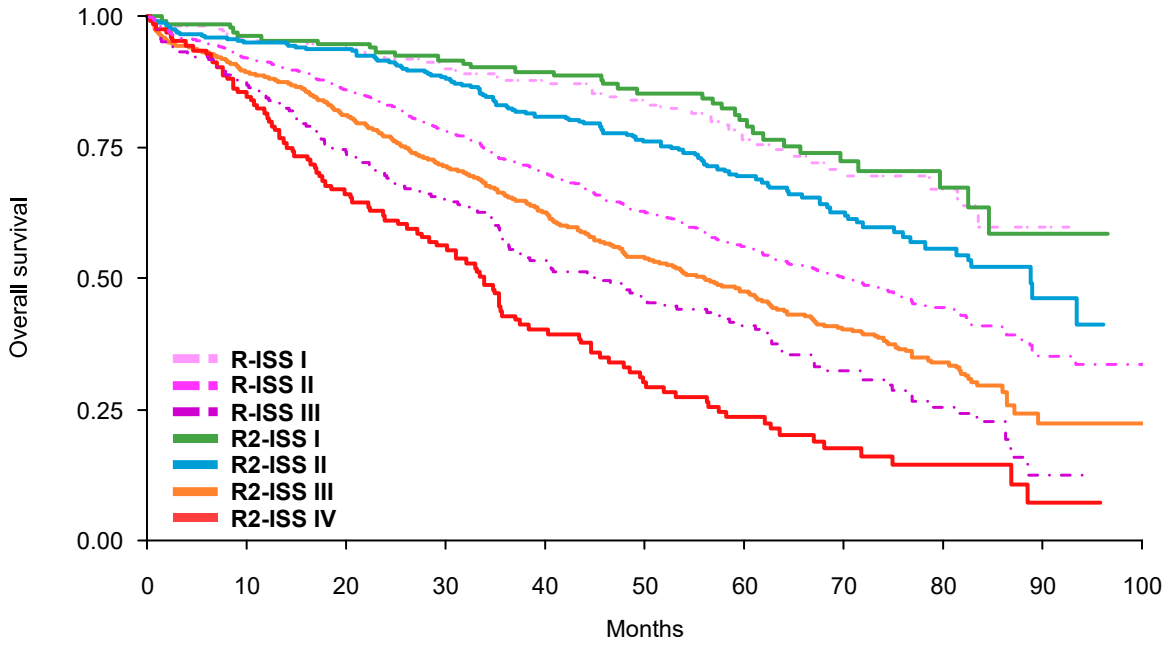
S6a. OS - Training set



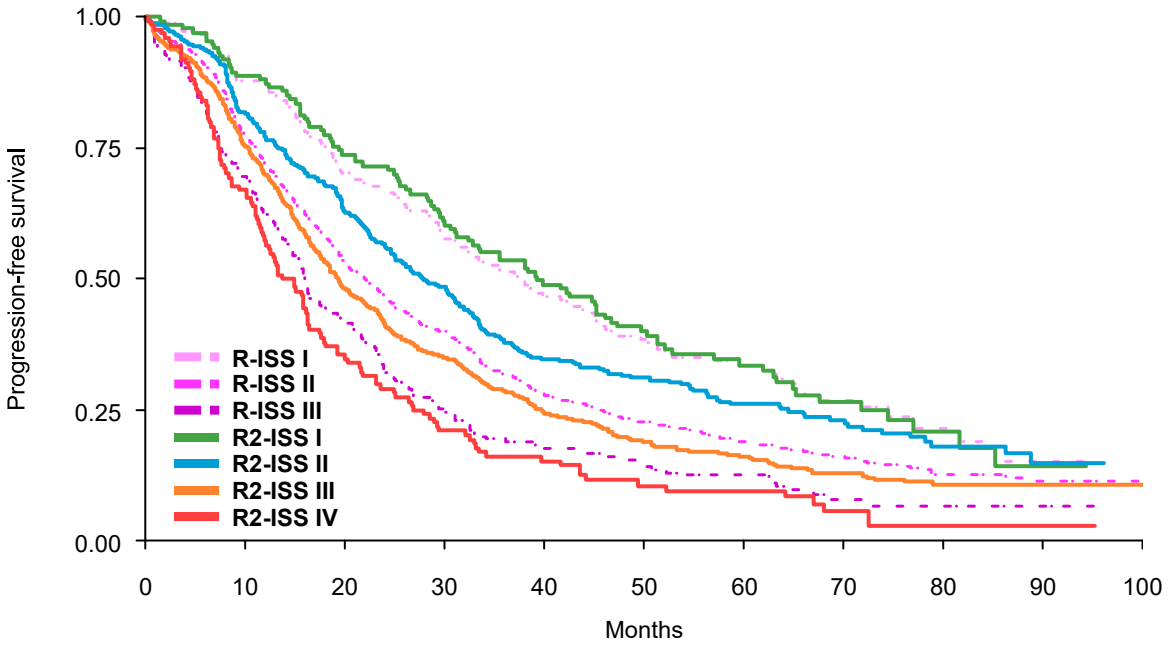
S6b. PFS - Training set



S6c. OS - Validation set



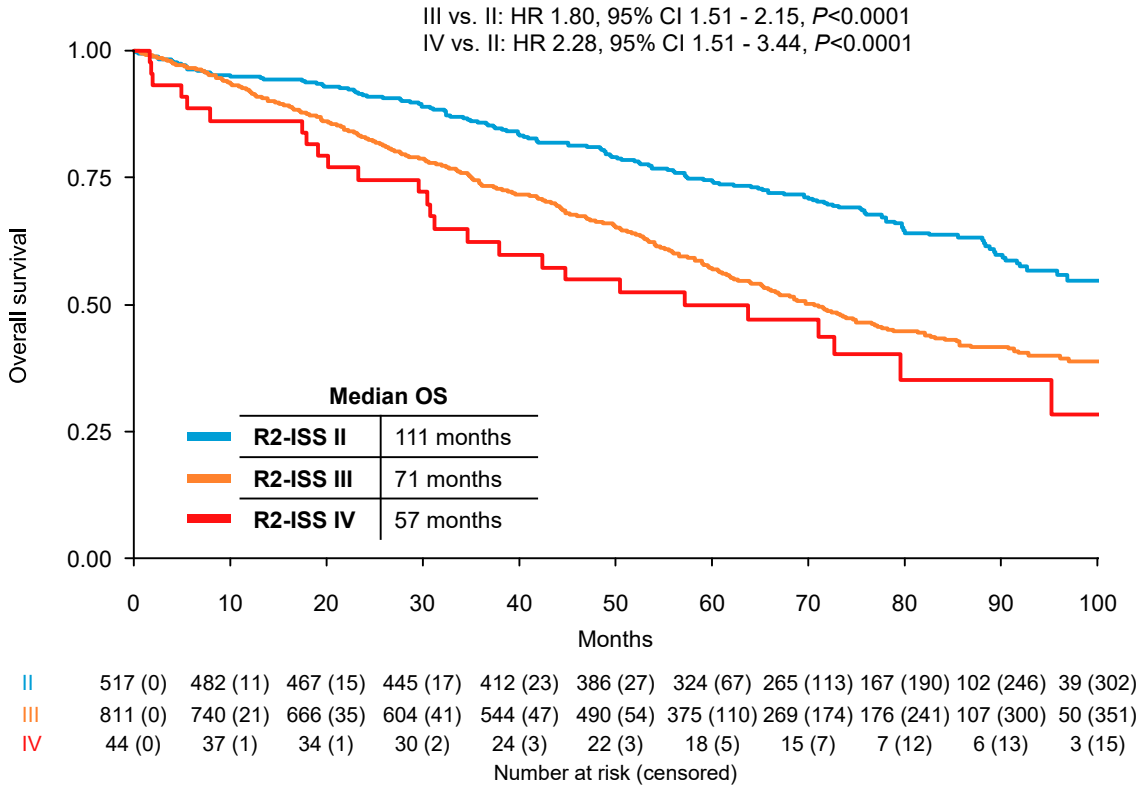
S6d. PFS - Validation set



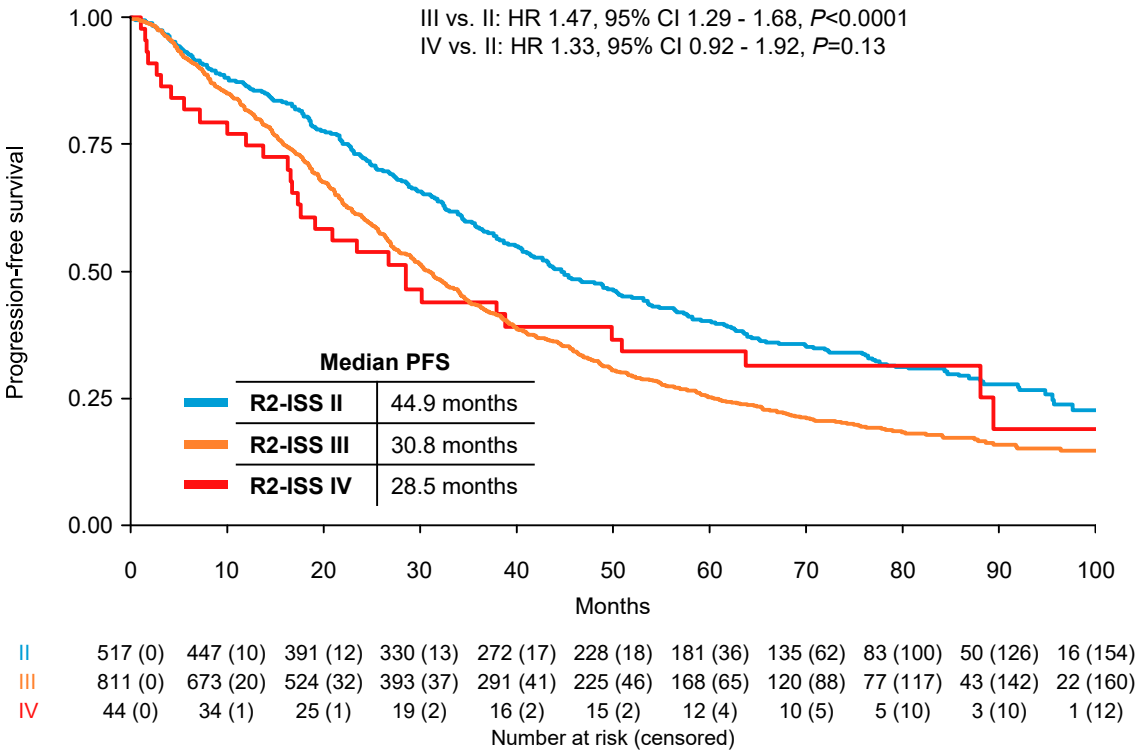
Abbreviations. OS, overall survival; PFS, progression-free survival; R2-ISS, Second Revision of the International Staging System; R-ISS, Revised International Staging System.

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

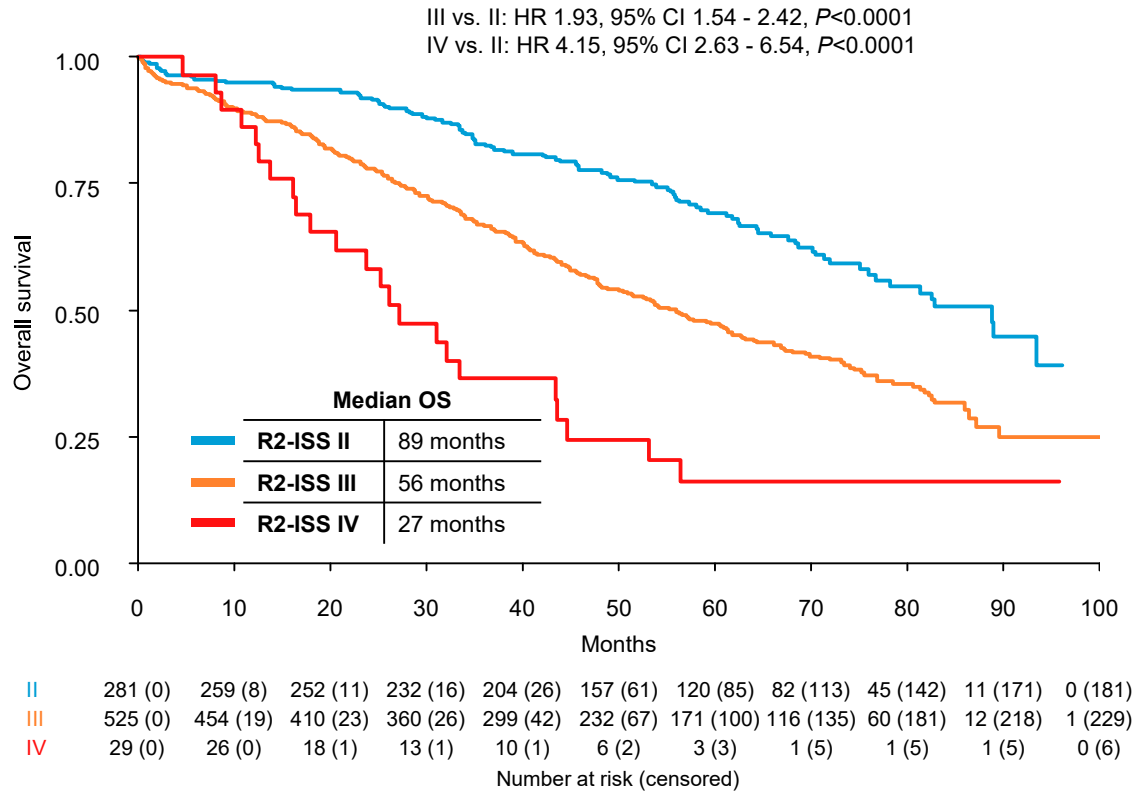
S7a. OS - Training set



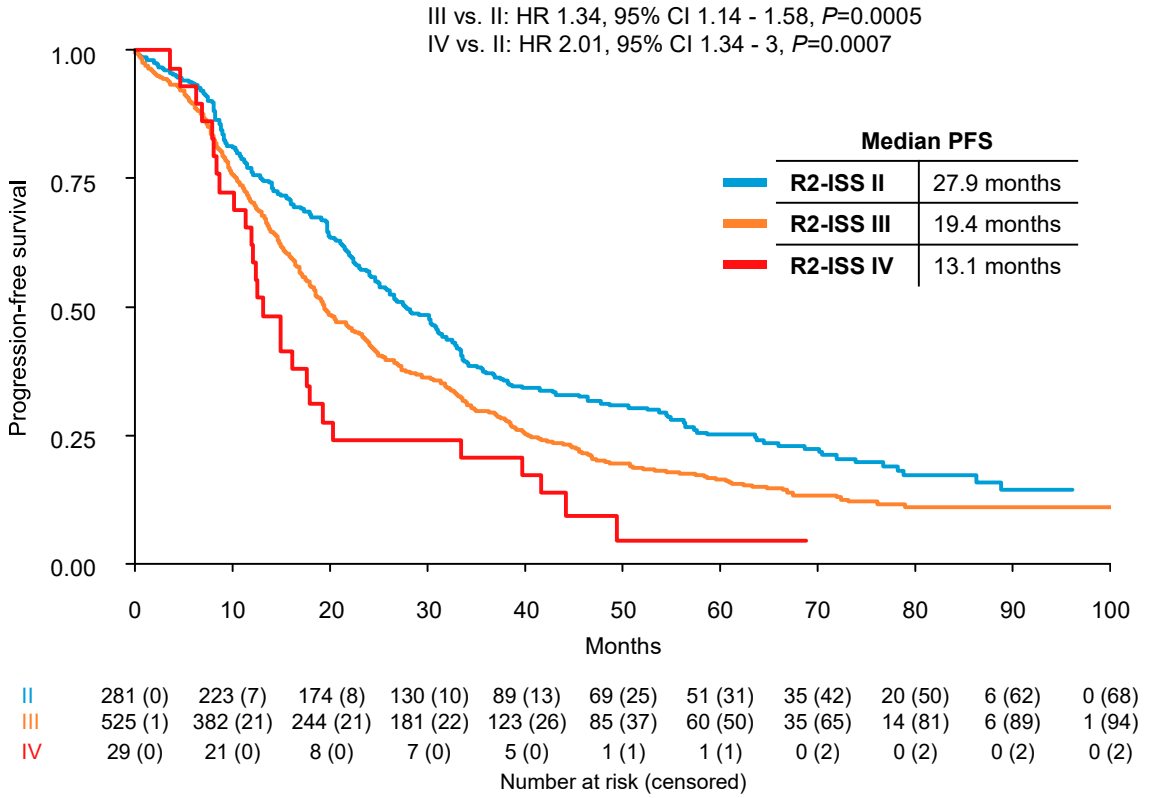
S7b. PFS - Training set



S7c. OS - Validation set

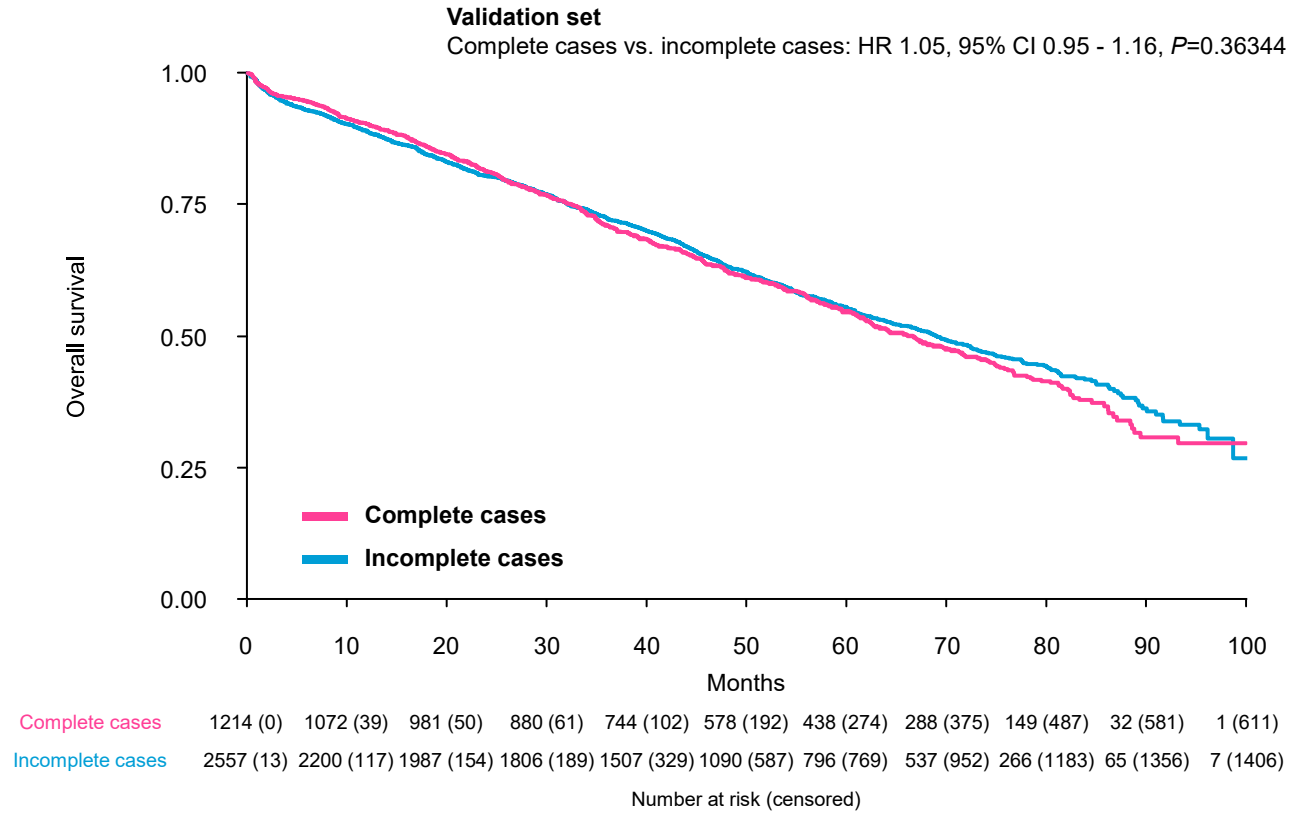


S7d. PFS - Validation set



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.

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