





# Development and validation of a novel risk stratification algorithm for relapsed multiple myeloma

Roman Hájek,<sup>1</sup>  Michel Delforge,<sup>2</sup> Marc S. Raab,<sup>3</sup>  Paul Schoen,<sup>4</sup> Lucy DeCosta,<sup>5</sup> Ivan Spicka,<sup>6</sup> Jakub Radocha,<sup>7</sup>  Ludek Pour,<sup>8</sup> Sebastian Gonzalez-McQuire<sup>4</sup> and Walter Bouwmeester<sup>9</sup> 

<sup>1</sup>Department of Haemato-oncology, University Hospital Ostrava, Ostrava, Czech Republic, <sup>2</sup>Department of Haematology, University Hospital Leuven, Leuven, Belgium, <sup>3</sup>Department of Internal Medicine V, University Hospital Heidelberg, Heidelberg, Germany, <sup>4</sup>Amgen Europe GmbH, Rotkreuz, Switzerland, <sup>5</sup>Amgen Ltd, Uxbridge, UK, <sup>6</sup>1st Medical Department – Clinical Department of Haematology, 1st Faculty of Medicine and General Teaching Hospital, Charles University, Prague, Hradec Králové, Czech Republic, <sup>7</sup>4th Department of Medicine - Haematology, Charles University Hospital and Faculty of Medicine Hradec Králové, Hradec Králové, Czech Republic, <sup>8</sup>Department of Internal Medicine, Haematology and Oncology, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic and <sup>9</sup>Pharmerit International, Rotterdam, the Netherlands

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Correspondence: Roman Hájek, Department of Haemato-oncology, University Hospital Ostrava, 17. listopadu 1790, 708 52 Ostrava, Czech Republic.  
E-mail: roman.hajek@fno.cz

Multiple myeloma (MM) is a malignancy of plasma cells that accounts for approximately 10% of all haematological cancers (Russell & Rajkumar, 2011; Vu *et al*, 2015; Moreau *et al*, 2017). MM is associated with considerable heterogeneity in terms of patient characteristics, drivers of disease progression, prognosis and treatment response (Moreau *et al*, 2017). This is exemplified by the variations observed in life

## Summary

Multiple myeloma (MM) is a malignancy with varying survival outcomes and drivers of disease progression. Existing MM staging tools were developed using data from newly diagnosed patients. As patient characteristics and disease-related factors change between diagnosis and the initiation of second-line (2L) treatment, an unmet need exists for a tool that can evaluate risk of death at first relapse. We have developed a risk stratification algorithm (RSA) using data from patients with MM who were at 2L. Hazard ratios for independent predictors of overall survival (OS) were derived from a Cox models, and individual patient scores were calculated for total risk. K-adaptive partitioning for survival was used to stratify patients into groups based on their scores. Relative risk doubled with ascending risk group; median OSs for patients in group 1 (lowest risk)–4 (highest risk) were 61.6, 29.6, 14.2 and 5.9 months, respectively. Differences in OS between risk groups were significant. Similar stratification was observed when the RSA was applied to an external validation data set. In conclusion, we have developed a validated RSA that can quantify total risk, frailty risk and disease aggressiveness risk, and stratify patients with MM at 2L into groups with profoundly different survival expectations.

**Keywords:** algorithm, multiple myeloma, overall survival, relapsed, risk stratification.

expectancy. The median overall survival (OS) for MM patients is in the range of 5–7 years; however, data suggest that 13% of patients die within 24 months of diagnosis (Fonseca *et al*, 2017) and findings from a European chart review suggested that 36% of patients with MM do not reach the second line of treatment (Raab *et al*, 2016). A tool that could accurately evaluate overall risk of death and identify

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the drivers of disease severity would be of considerable value, especially at first relapse when patient and disease-related information is available.

The International Staging System (ISS; Greipp *et al*, 2005) and the Revised International Staging System (R-ISS; Palumbo *et al*, 2015a) are used to define disease progression in patients with MM. Clinical trial data from over 10 000 patients newly diagnosed with MM were used to develop the ISS, in which patients were stratified into one of three risk groups based on serum albumin and serum  $\beta$ -2 microglobulin ( $\text{S}\beta$ 2M) levels (Greipp *et al*, 2005). In the following years, studies highlighted the link between the presence of specific cytogenetic abnormalities (CA; del[17p], t[4;14] and t[14;16]), increased lactate dehydrogenase (LDH) levels and reduced OS (Fonseca *et al*, 2009; Terpos *et al*, 2010; Ross *et al*, 2012). To reflect this, the International Myeloma Working Group (IMWG) published a position paper in which three risk groups were defined based on the ISS criteria and CA at diagnosis (Chng *et al*, 2014); a revised ISS (R-ISS) was published in 2015, in which CA and LDH levels were taken into account in addition to  $\text{S}\beta$ 2M and serum albumin levels (Palumbo *et al*, 2015a). The ISS and R-ISS have been widely adopted in clinic practice and clinical trials (Lonial *et al*, 2015; Stewart *et al*, 2015; Moreau *et al*, 2016; Dimopoulos *et al*, 2016a). It should be noted, however, that both tools were developed to stage patients using only information available at diagnosis, and neither tool has been fully validated in the relapse setting or takes patient frailty into consideration.

There is a need for physicians to assess patient prognosis systematically using all available evidence when making treatment decisions at the initiation of second-line (2L) treatment. This has become particularly important in the past decade owing to the dramatic rise in the number of agents that have been approved for patients with relapsed or refractory MM (RRMM) (carfilzomib, Amgen Europe, Dublin, Ireland; elotuzumab, Bristol-Myers Squibb S.r.l., Anagni, Italy; pomalidomide, Celgene Distribution B.V., Utrecht, Netherlands; daratumumab and bortezomib, Janssen Biologics B.V., Leiden, The Netherlands; ixazomib, Takeda GmbH, Singen, Germany). In the absence of a more suitable algorithm, the R-ISS and ISS are frequently used to stratify patients with MM at relapse in clinical trials (Lonial *et al*, 2015; Moreau *et al*, 2016; Palumbo *et al*, 2016; Dimopoulos *et al*, 2016a; Dimopoulos *et al*, 2016b). In practice, however, the value of considering R-ISS or ISS stage when making treatment decisions following first relapse is unclear. It is widely accepted that when making treatment decisions at 2L, physicians need to consider a range of patient and disease characteristics and experiences during first-line (1L) treatment; therefore, any tool developed to stratify patients at this disease stage should reflect this thought process (Bird *et al*, 2011; Sonneveld & Broijl, 2016; Moreau *et al*, 2017). A recent analysis of real-world data from patients with MM revealed that patient characteristics and predictors of OS differed between

the initiation of 1L and 2L treatments (Hájek *et al*, 2016). Moreover, the predictors of OS at 2L included parameters that were based on information that was revealed during 1L therapy (Hájek *et al*, 2016). Herein, we describe the development and validation of a novel risk stratification algorithm (RSA) that can systematically assess the risk of death as well as the factors driving risk, such as frailty, whilst also reflecting the physician's thought process when defining patient prognosis at first relapse. In addition, we present an interpretation of the results obtained from implementation of the RSA.

## Materials and methods

### Data source

*Model development cohort.* The Czech Registry of Monoclonal Gammopathies (RMG) is one of the largest registries of patients with MM and monoclonal gammopathies of unknown significance. It contains detailed data on a large number of patient characteristics and disease-related parameters recorded at diagnosis and at first relapse. In addition, the RMG has mature OS data and is representative of the national and international patient populations. For these reasons, the RMG was selected for development of the RSA (Radocha *et al*, 2015). Data were collected from all 20 of the Czech centres that actively treat patients with MM; these centres cover approximately 80% of all patients with MM in the Czech Republic (Radocha *et al*, 2015). Data collection began in May 2007, and patients were observed from diagnosis until either death, loss to follow-up or 26 April 2016.

### Eligibility criteria

Because there is an unmet need to re-define patients' survival expectations at first relapse, the current analysis only included individuals aged 18 years or older who received at least one dose of anti-myeloma treatment following first relapse. Patients who died or were lost to follow-up before initiating 2L treatment were excluded from the analysis.

### Development strategy

*Step 1: identification of candidate predictors of overall survival at initiation of second line.* Candidate predictors of OS were identified based on literature analyses, and the findings from a conceptual model of MM progression that was defined by a Delphi process involving leading experts in MM (Fig 1) (Gonzalez-McQuire *et al*, 2019).

*Step 2: defining parameters to reflect clinical relevance.* Predictors were classified into one of four types based on how the parameters were associated with risk of death: categorical in nature (e.g. presence of extramedullary disease);

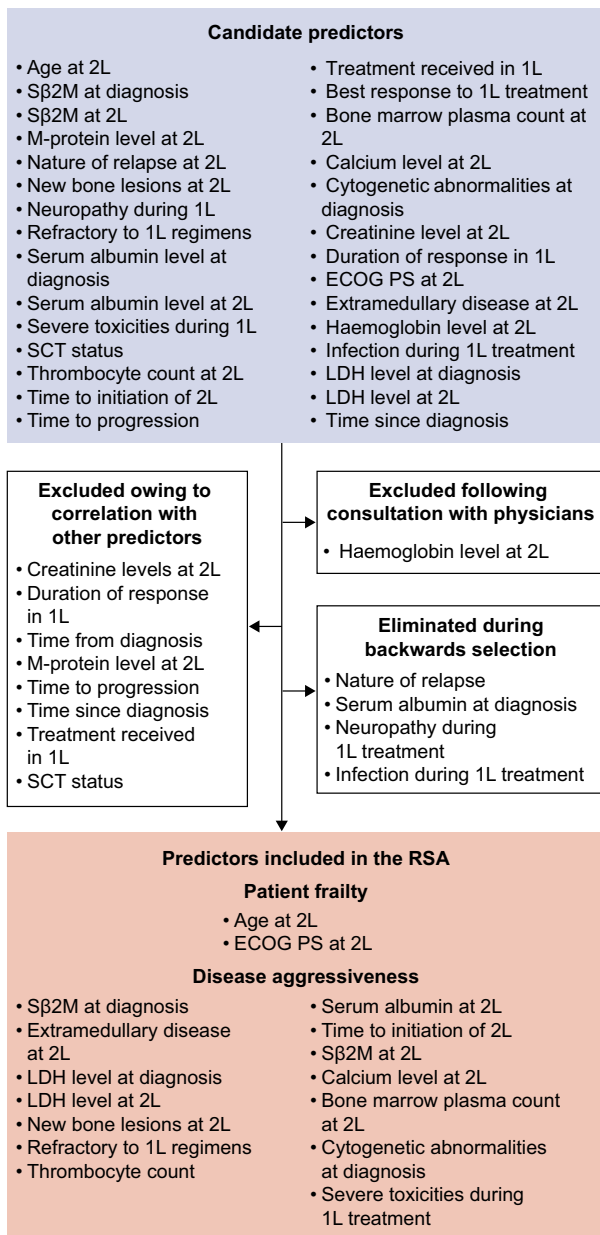


Fig 1. Selection of predictors for the risk stratification algorithm. 1L, first line; 2L, second line; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; RSA, risk stratification algorithm; Sβ2M, serum β-2 microglobulin; SCT, stem cell transplantation.

continuous with established clinical cut-offs (e.g. LDH level), which were treated as categorical predictors; continuous up to a threshold point beyond which the risk of death remained constant (e.g. thrombocyte count); and fully continuous (e.g. age).

Time to initiation of 2L treatment was treated as a categorical, dichotomized variable (>24 months vs. ≤24 months). A boundary of 2 years may be regarded as too high and applicable only to patients with a good prognosis. However, time to

initiation of 2L treatment is strongly influenced by treatment decisions, and a short time to initiation of 2L treatment may not correspond to a poor prognosis. Therefore, a high cut-off level (24 months) was selected to allow the positive impact on prognosis associated with a longer time to initiation of 2L treatment to be captured. Other predictors, such as refractory status, occurrence of grade 3 or 4 adverse events (AE) and presence of hypercalcaemia or extramedullary disease, are likely to capture the increased risk of death associated with short time to initiation of 2L treatment.

Multiple imputation was used to estimate missing values for all variables except presence of CA (Eisemann *et al*, 2011). A category of 'not available' was included for CA to reflect clinical practice, in which CA data are not available for large numbers of patients, some of whom will have high-risk CA, and risk CA (Groenwold *et al*, 2012).

*Step 3: selecting the significant predictors of overall survival at the initiation of second line.* To select the final predictors, Pearson's correlations test identified and excluded the factors that correlated strongly with other parameters. The remaining predictors entered multivariable Cox regression models, in which OS from initiation of 2L treatment was the dependent variable. A backward selection was performed using Akaike's information criterion (AIC).

One of the known disadvantages of predictor selection based on statistical analyses, such as backward selection, is the exclusion of known risk factors (Austin & Tu, 2004). Therefore, to ensure that the RSA included key parameters that are known to define disease severity and to reflect a physician's thought process when selecting a 2L treatment, it was decided that the following predictors would be included in the model regardless of statistical significance: age, Sβ2M level, LDH level, Eastern Cooperative Oncology Group (ECOG) performance status (PS) (at initiation of 2L in all cases), time to initiation of 2L, refractory status and cytogenetic risk at diagnosis. High cytogenetic risk was defined as presence of del (17p) and/or translocation t (4;14) and/or t (14;16).

*Step 4: calculating patient-specific risk scores.* The overall score for each patient was obtained by multiplying the hazard ratios (HRs) corresponding to the patient-specific value for each parameter. Multiplying the risk scores, means that each score represents a relative increase in risk of death compared with a patient who has the lowest/lower risk for all predictors.

*Step 5: defining risk stratification using patient-specific risk score.* The methodology required us to assume that four risk groups would be defined, and no group would contain less than 10% of the analysis population (unpublished observations). A K-adaptive partitioning for survival (KAPS) algorithm was used to analyse the survival data and risk scores to determine whether patients could be partitioned into groups

with statistically significant differences in survival expectations. KAPS was used in the development of the R-ISS and has been applied to the Surveillance, Epidemiology and End Results Program run by the National Institutes of Health (Eo *et al*, 2014; Palumbo *et al*, 2015a).

*Steps 6: defining the drivers of risk.* To develop an understanding of the factors that drive risk in patients with MM at the initiation of 2L, the predictors were separated into those associated with patient frailty and those related to disease aggressiveness. While several definitions of frailty exist (Ethun *et al*, 2017), for this analysis frailty was defined as a measure of ECOG PS and age. Through multiplying the HR associated with the predictors in each subset, patient-specific risk scores were obtained for frailty and disease aggressiveness.

*Step 7: understanding the influence of second-line treatment on prognosis.* Treatment received during 2L was not a candidate predictor because the RSA aims to provide physicians with an insight into the appropriate management of patients at first relapse. In addition, adjusting for future variables can result in biased results (Cole *et al*, 2010). It was assumed that all patients with MM in the Czech RMG would receive the most effective, suitable treatment available. However, second-line treatment patterns by risk group and the impact of treatment used in 2L on survival expectations were analysed descriptively.

### Validation

The RSA was tested in an external data set containing information on patients with symptomatic MM from France, Germany and the UK who initiated 2L therapy in 2013. In total, 180 physicians were involved in a specially designed retrospective chart review study. The data were derived from patient medical chart audits based on a questionnaire sent to physicians. Regional and hospital type quotas were applied to ensure a representative sample. Further information on hospital type and region can be found in Table SI. Relevant data were abstracted onto a study-specific case report form during the second and third quarters of 2017. The RSA was applied to the validation data set in the same manner as it was applied to the Czech RMG. To evaluate the performance of the RSA in the external data set, Harrell's overall concordance index (C-index) was calculated (which indicates the proportion of pairs of subjects whose observed and predicted outcomes agree).

## Results

### Patient baseline characteristics

*Development cohort.* Data from 1418 patients in the Czech RMG were included in the analysis. The median duration of

follow-up was 27.56 months (95% confidence interval [CI]: 25.05–30.09) (taking into account censoring owing to mortality), and the mean follow-up was 38.34 months (95% CI: 36.06–40.61). The baseline characteristics of this cohort reflect the heterogeneous nature of the global real-world MM population (Table I). At the initiation of 2L treatment, over one-fifth (21%) of patients were over 75 years of age, approximately three-quarters (74%) had an ECOG PS of 0 or 1, and 70% had progressed within 24 months of initiating 1L treatment. Approximately one-third (35%) of patients received proteasome inhibitors at 1L, 44% were treated with immunomodulators, and 6% received a combination containing both classes of agent.

*Validation cohort.* Chart data from 998 patients were collected; the baseline characteristics are presented in Table I. When initiating 2L treatment, 17.3% of patients in the validation set were aged over 75 years, 71% had an ECOG PS of 0 or 1, and over half (53%) had initiated 2L treatment within two years of diagnosis. Of note, fewer patients in the validation set had experienced a grade 3 or 4 toxicity during or before 1L treatment than in the development set (11.9% vs. 52.2%).

### Predictors of overall survival included in the risk stratification algorithm

Of the 29 pre-selected candidate parameters, 16 were identified as independent predictors of OS following Pearson's correlation test and a Cox regression analysis (Fig 1 and Table II). Although they are considered to be important variables when predicting risk in patients with MM, creatinine level, time since diagnosis, time to progression (TTP), treatment regimen in 1L, duration and depth of response, M protein level and stem cell transplantation status were excluded because they correlated with other stronger predictors of OS. Infection and neuropathy (during 1L treatment), serum albumin at diagnosis and nature of relapse were eliminated during the backward selection process. Haemoglobin level was removed as a predictor following guidance from physicians because low levels are not considered to be indicative of disease severity.

The 16 predictors were split into those associated with patient frailty (age and ECOG PS) and those that describe disease aggressiveness (all other predictors, including patient's experience during 1L treatment). These predictors reflect factors that should be considered when defining patient-specific disease severity: characteristics at diagnosis (3 predictors), characteristics at the initiation of 2L treatment (10 predictors) and patient's experience during 1L treatment (3 predictors) (Table II). CA are not routinely reassessed at relapse, so CA status at diagnosis was used as a predictor of OS, rather CA status at the initiation of 2L. Of the prespecified parameters that would be included in the RSA regardless of significance, only time to initiation of 2L treatment was forced into the



**Table I.** Characteristics of patients in development and validation cohorts.

Characteristic*	Czech RMG (N = 1418)	Validation dataset (N = 998)
Age (years)		
<65	494 (34.8%)	422 (42.3%)
65–75	624 (44.0%)	403 (40.4%)
>75	300 (21.2%)	173 (17.3%)
Mean (SD)	67.4 (9.8)	66.4 (10.2)
Median (IQR)	68.0 (61.0–74.0)	67.0 (59–74)
β2 microglobulin (mg/l)		
<3.5	648 (45.7%)	339 (34.0%)
3.5–5.5	370 (26.1%)	405 (40.6%)
>5.5	400 (28.2%)	254 (25.5%)
Mean (SD)	5.7 (6.8)	4.5 (2.5)
Median (IQR)	3.7 (2.6–5.8)	3.9 (3.0–5.6)
β2 microglobulin at diagnosis (mg/l)		
<3.5	548 (38.6%)	369 (37.0%)
3.5–5.5	392 (27.6%)	389 (39.0%)
>5.5	478 (33.7%)	240 (24.0%)
Mean (SD)	6.3 (6.8%)	4.4 (2.3)
Median (IQR)	4.2 (2.8–6.6)	3.9 (3.0–5.5)
Albumin (g/dl)		
<3.5	275 (19.4%)	509 (51.0%)
≥3.5	1143 (80.6%)	489 (49.0%)
Mean (SD)	4.0 (0.6)	3.5 (0.9)
Median (IQR)	4.1 (3.7–4.4)	3.4 (3.0–3.8)
CA at diagnosis		
Standard risk	95 (6.7%)	332 (33.3%)
High risk	175 (12.3%)	209 (20.9%)
NA†	1148 (81.0%)	457 (45.8%)
LDH (U/l)		
≤360	1280 (90.3%)	744 (74.5%)
>360	138 (9.7%)	254 (25.5%)
Mean (SD)	262.3 (311.6)	302.7 (147.3)
Median (IQR)	205.4 (167.7–267.1)	246 (201–361)
LDH at diagnosis (U/l)		
≤360	1338 (94.4%)	784 (78.6%)
>360	80 (5.6%)	214 (21.4%)
Mean (SD)	210.7 (142.5)	296 (157.8)
Median (IQR)	183.8 (150.3–232.3)	246 (200–350)
ECOG performance status		
0	213 (15.0%)	144 (14.4%)
1	838 (59.1%)	566 (56.7%)
2	279 (19.7%)	258 (25.9%)
3–4	88 (6.2%)	30 (3.0%)
Thrombocyte count (× 10 <sup>9</sup> /l)		
>100	1271 (89.6%)	867 (86.9%)
≤100	147 (10.4%)	131 (13.1%)
Mean (SD)	193.7 (85.2)	180.3 (79.4)
Median (IQR)	185.0 (139.0–236.0)	176 (121–212)
Hypercalcaemia		
No (calcium ≤2.75 mmol/l)	1360 (95.9%)	705 (70.6%)
Yes (calcium >2.75 mmol/l)	58 (4.1%)	293 (29.4%)
Mean (SD)	2.3 (0.3)	3.4 (2.6)
Median (IQR)	2.3 (2.2–2.4)	2.4 (2.2–2.9)

**Table I.** (Continued)

Characteristic*	Czech RMG (N = 1418)	Validation dataset (N = 998)
Bone marrow plasma cell count (%)		
<20	760 (53.6%)	240 (24.0%)
20–70	552 (38.9%)	668 (66.9%)
>70	106 (7.5%)	90 (9.0%)
Mean (SD)	23.7 (25.4)	36.6 (22.7)
Median (IQR)	17.6 (0.0–37.5)	32 (20.0–50.0)
Extramedullary disease		
No	1257 (88.6%)	879 (88.1%)
Yes	161 (11.4%)	119 (11.9%)
Time to initiation of 2L treatment (months)		
>24	415 (29.3%)	467 (46.8%)
≤24	1003 (70.7%)	531 (53.2%)
Refractory to previous treatment		
Non-refractory/refractory to other regimens without new drugs	1083 (76.4%)	787 (78.9%)
Refractory to bortezomib	149 (10.5%)	123 (12.3%)
Refractory to thalidomide	142 (10.0%)	1 (0.1%)
Refractory to other regimens with new drugs <sup>§</sup>	44 (3.1%)‡	87 (8.7%)
New bone lesions		
No new lesions	410 (28.9%)	396 (39.7%)
>2 lesions at diagnosis and at 2L, or new lesions	1008 (71.1%)	602 (60.3%)
NA	–	–
Severe toxicities during/before 1L treatment (highest grade experienced)		
0–2	635 (44.8%)	879 (88.1%)
3 or 4	783 (55.2%)	119 (11.9%)
Prior 1L therapy		
Bortezomib only	499 (35.2%)	479 (48.0%)
Thalidomide only	549 (38.7%)	259 (26.0%)
Bortezomib and thalidomide	66 (4.7%)	110 (11.0%)
Bortezomib and lenalidomide	14 (1.0%)	10 (1.0%)
Lenalidomide	75 (5.3%)	30 (3.0%)
Other with new drugs	93 (6.6%)	262 (26.2%)
Other without new drugs	211 (14.9%)	103 (10.3%)

Data are *n* (%) unless stated otherwise.

1L, first-line; 2L, second-line; CA, cytogenetic abnormalities; ECOG, Eastern Cooperative Oncology Group; IQR, inter-quartile range; LDH, lactate dehydrogenase; NA, not available; RMG, Registry of Monoclonal Gammopathies; SD, standard deviation.

\*As measured at the initiation of 2L treatment unless otherwise stated.

†Missing values were not imputed for cytogenetic abnormalities.

‡‘New’ drugs include carfilzomib, daratumumab, elotuzumab, ixazomib, panobinostat, pomalidomide and thalidomide.

§Refractory to other regimens with new drugs – includes bortezomib plus thalidomide, lenalidomide only, bortezomib plus lenalidomide, and lenalidomide plus thalidomide.

Table II. Predictors of overall survival at 2L (Cox regression analysis).

Predictor of overall survival*	Classification of predictor	Categories/thresholds	Backward selection	P value
			HR (95% CI) AIC = 9172.275	
Age (years)	Fully continuous	NA	1.015 (1.007–1.023)†	0.0002
Albumin (g/dl)	Fully continuous	NA	0.846 (0.745–0.960)†	0.0095
Bone marrow plasma cell count (%)	Fully continuous	NA	1.008 (1.005–1.011)†	<0.0001
Thrombocyte count ( $\times 10^9/l$ )	Continuous with threshold	( $150 \times 10^9/cells$ )	0.995 (0.992–0.997)†	<0.0001
S $\beta$ 2M (mg/l)	Continuous with threshold	(5.5 mg/l)	1.063 (0.993–1.138)†	0.0787
S $\beta$ 2M at diagnosis (mg/l)	Continuous with threshold	(5.5 mg/l)	1.090 (1.022–1.162)†	0.0084
LDH (U/l)	Continuous with clinically established cut-offs	$\leq$ ULN >ULN	Reference 2.080 (1.651–2.622)	<0.0001
LDH at diagnosis (U/l)	Continuous with clinically established cut-off	$\leq$ 360‡ >360	Reference 1.297 (0.960–1.752)	0.0904
Calcium (mmol/l)	Continuous with clinically established cut-off	$\leq$ 2.75 >2.75	Reference 1.406 (1.012–1.954)	0.0422
Time to next treatment (months)	Continuous with clinically established cut-off	>24 $\leq$ 24	Reference 1.112 (0.915–1.353)	0.2858
ECOG performance status	Categorical	0 1 2 3 or 4	Reference 1.667 (1.227–2.265) 2.123 (1.520–2.964) 3.708 (2.496–5.506)	 0.0011 <0.0001 <0.0001
CA at diagnosis	Categorical	Standard risk High risk NA	Reference 1.643 (1.147–2.353) 1.081 (0.789–1.481)	 0.0067 0.6299
Extramedullary disease	Categorical	No Yes	Reference 2.331 (1.872–2.904)	<0.0001
New bone lesions (X-ray)	Categorical	No new lesions >2 at diagnosis and initiation of 2L§ or new lesions	Reference 1.271 (1.075–1.502)	0.0049
Refractory status	Categorical	Non-refractory Refractory to bortezomib Refractory to thalidomide Refractory regimens with new agents¶	Reference 1.533 (1.202–1.955) 1.186 (0.942–1.493) 1.427 (0.961–2.120)	 0.0006 0.1446 0.0776
Severe toxicities during 1L treatment (any grade 3 or 4 toxicity)	Categorical	No Yes	Reference 1.145 (0.984–1.332)	0.0797

1L, first line; 2L, second line; AIC, Akaike's information criterion; CA, cytogenetic abnormalities; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; NA, not available; S $\beta$ 2M, serum  $\beta$ -2 microglobulin; ULN, upper limit of normal.

\*At initiation of 2L treatment unless otherwise stated.

†HR per unit change.

‡ULN was 360 U/l in this data set.

§Category comprises patients with accelerated osteoporosis/>2 lesions at diagnosis and 2L.

¶Comprising bortezomib plus thalidomide ( $n = 21$ ), lenalidomide only ( $n = 20$ ), bortezomib plus lenalidomide ( $n = 2$ ) and lenalidomide plus thalidomide ( $n = 1$ ); two patients were recategorized based on known previous treatment.

model. The risk score calculation for a theoretical patient entering 2L treatment is shown in Table III.

### Patient-specific risk scores

**Development cohort.** The KAPS defined four distinct patient groups based on survival expectations and total risk scores (Fig 2). Risk Group 2 contained the largest proportion of patients ( $n = 596$ ; 42%), followed by Group 1 ( $n = 351$ ;

25%) and then Group 3 ( $n = 318$ ; 22%); Group 4 contained the smallest number of patients ( $n = 153$ ; 11%). As specified by the methodology, no groups contained less than 10% of the analysis population (Fig 2). The calculation formula to measure risk score is included in Appendix S1.

**Validation cohort.** When the RSA was applied to the validation cohort, 17.8% of patients were placed in Risk Group 1,

**Table III.** Calculation of risk scores for a theoretical patient entering 2L treatment.

Parameter (at initiation of 2L unless stated otherwise)	Value	Calculation	HR for calculating risk scores	
Age	72 years	$\exp(0.015 \times 72)$	2.945	
ECOG PS	1	NA	1.667	
<i>Frailty risk score</i>			4.9	
S $\beta$ 2M	3.5 mg/l	$\exp(0.061 \times 3.5)$	1.238	
S $\beta$ 2M at diagnosis	5.5 mg/l	$\exp(0.086 \times 5.5)$	1.605	
CA at diagnosis	Standard risk	NA	1	
Calcium	>2.75 mmol/l		1.406	
LDH	Below ULN	NA	1	
LDH at diagnosis	Below ULN	NA	1	
Extramedullary disease	No		1	
New bone lesions	No		1	
Serum albumin	3.8 g/l	$\exp(-0.168 \times 3.8)$	0.528	
Thrombocyte count	$220 \times 10^9/l$	$\exp(-0.005 \times 150)$	0.472	
Bone marrow plasma count	65%	$\exp(0.008 \times 65)$	1.682	
Time to next treatment	>24 months		1	
Refractory status	Refractory to bortezomib		1.533	
Severe toxicities in 1L	No		1	
<i>Disease aggressiveness risk score</i>			2.0	
<i>Total risk score</i>			9.8	
<i>Theoretical patient risk group classification</i>			3	
<i>Total risk score cut-off values for classification</i>	<i>Group 1</i>	<i>Group 2</i>	<i>Group 3</i>	<i>Group 4</i>
	<i>Min</i>	<i>Min</i>	<i>Min</i>	<i>Min</i>
	<i>Max</i>	<i>Max</i>	<i>Max</i>	<i>Max</i>
	–	>3	>7	>15.4
	$\leq 3$	$\leq 7$	$\leq 15.4$	–

1L, first line; 2L, second line; CA, cytogenetic abnormalities; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; NA, not available; S $\beta$ 2M, serum 2-microglobulin; ULN, upper limit of normal.

34.6% were in Risk Group 2, 24.9% were in Group 3, and 22.6% were in Group 4 (Fig 2B).

### Overall survival by risk group

**Development cohort.** The differences in median OS from the initiation of 2L treatment between groups were statistically significant. The median OS halved, and the risk of death doubled with ascending risk group. The OSs for patients in Risk Groups 1–4 were 61.6, 29.6, 14.2 and 5.9 months, respectively (Figure S1), and the HRs for differences in OS between Group 1 and Groups 2, 3 and 4 were 2.24, 4.30 and 10.88, respectively ( $P > 0.001$  in all cases), with no overlap in the associated 95% CI (Fig 3).

**Validation cohort.** The median OS was not reached for patients assigned to Groups 1 and 2, 39.9 months in Risk Group 3 and 16.2 months for those in Risk Group 4. The HRs for the differences in OS between patients in Group 1 and those in Groups 2, 3 and 4 were 1.87, 4.61 and 8.51, respectively (Fig 2B). The C-index when the RSA was applied to the external data set was 0.715 (95% CI: 0.69–0.74) (a

score of 0.5 represents total random predictions; a perfectly discriminating model would have a score of 1) (Harrell, 2001).

### Drivers of risk of death

To provide a deeper understanding of patients' needs when initiating 2L treatment, risk scores for patients in the development cohort were assigned based on the two groups of predictors: those associated with patient frailty and those that describe disease aggressiveness. Mean frailty risk scores increased from 3.7 in Group 1 to 6.9 in Group 4; the differences between risk groups were greater still for mean disease aggressiveness scores (0.6 in Group 1 vs. 4.9 in Group 4; Figure S1).

Plotting frailty risk score against disease aggressiveness risk scores provides a graphic illustration of the factors driving risk for individual patients in addition to the total risk score. As can be seen in Fig 3, both disease aggressiveness and patient frailty contribute to risk of death for the majority of patients. However, a closer inspection of the data showed that a subset of patients in Risk Group 4

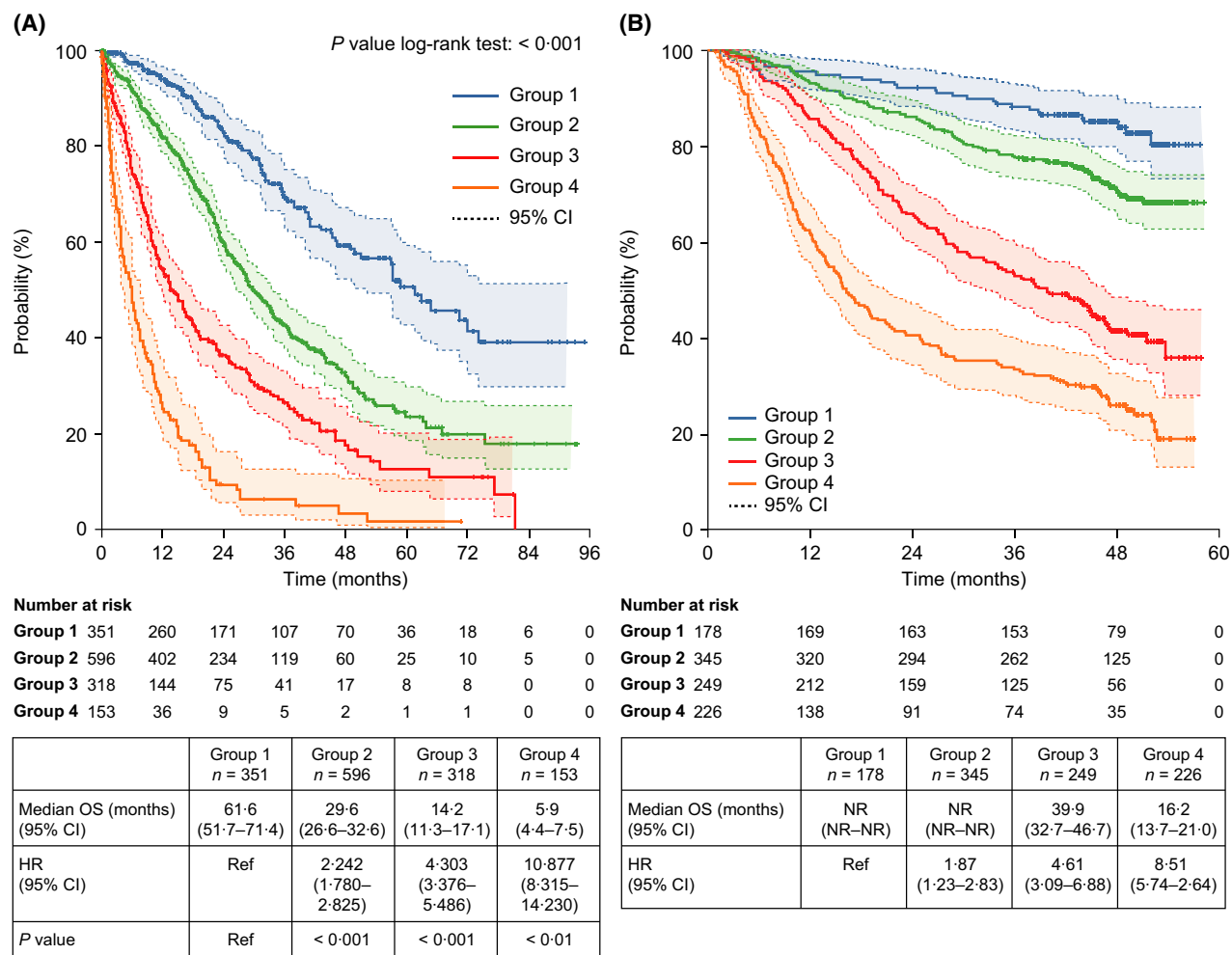


Fig 2. Overall survival stratified by risk group (A) development cohort; (B) validation cohort. CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; Ref, reference.

(shaded area A) did not have aggressive disease, and the high risk was driven by frailty alone. In contrast, shaded area B shows a population of patients in Risk Group 4 with low frailty risk scores whose poor survival expectations were driven by the particularly aggressive nature of their disease.

#### Patient characteristics by risk group

Exploring the characteristics of patients in each risk group of the development cohort showed that no single predictor governed underlying risk of death at the initiation of 2L treatment. For example, of the patients in Risk Group 4, 32 were aged 65 years or below, and 52% had LDH levels below the upper limit of normal. Of the patients in Risk Group 1, however, 45% of evaluable patients had high-risk CA, and 46% had 3 or 4 AE at grade 3 or 4 during 1L treatment (Table SII).

#### Other treatment outcomes by risk group

Although the RSA was developed to predict OS, the stratification also holds for progression-free survival (PFS) and TTP in the development cohort. Patients in Risk Groups 1–4 experienced a median PFS of 18.1, 13.2, 8.3 and 3.4 months, respectively, and a median TTP of 18.9, 14.1, 9.5 and 3.7 months, respectively (Table SIII). The proportions of patients in Groups 1–4 who achieved a very good partial response (VGPR), or better, during treatment were 29%, 24%, 19% and 13%, respectively (Table SIII).

*Development cohort.* Treatment patterns were similar across risk groups, suggesting that physicians in the Czech Republic were not making treatment choices based on risk (Table SIII). OS outcomes were broadly similar for each group regardless of treatment used. Among patients with the same regimen, OS expectation increased with increasing risk group.



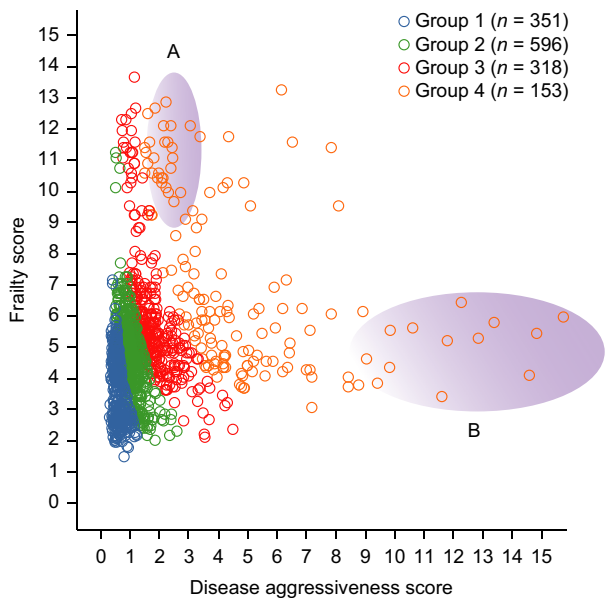


Fig 3. Patient frailty risk scores *versus* disease aggressiveness risk scores. Scores over 15 for disease aggressiveness have been excluded ( $n = 3$ ).

**Validation cohort.** Lenalidomide-based regimens were the most common treatment choice for patients in each of the risk groups (43.8% in Group 3 to 57.1% in Group 4) and bortezomib-based regimens were the second most frequently used treatment (24.3% in group 4–40.6% in Group 3). There was a trend for new drugs to be used more commonly in the lower-risk groups (9.6%, 9.3%, 5.6% and 4.0% in Groups 1–4, respectively), whilst old drugs were used more in higher-risk groups (3.9%, 4.3%, 6.4% and 10.2% in Groups 1–4, respectively) (Table SIII).

## Discussion

The RSA defines four groups with significantly different OS from the initiation of 2L treatment. In addition, the algorithm also allows the physician to identify the drivers of disease in terms of patient frailty or disease aggressiveness on an individual basis for the first time. Existing risk stratification tools for MM were primarily developed using clinical trial data from newly diagnosed patients and used a small number of disease-related predictors. The validated analysis presented here demonstrated that to assess systematically and quantify appropriately the total risk and the drivers of risk, more information is needed regarding patients' experiences during 1L and during clinical presentation at the initiation of 2L therapy.

Existing staging tools for patients with MM (ISS and R-ISS) have not been validated in the relapse setting using real-world data and may therefore be of limited value to medical decision-making at first relapse. Evidence from a European retrospective chart review of deceased patients with MM

suggests that using the R-ISS stage alone is not a reliable way to predict prognosis in real-world patient populations. The study reported that 8% of patients with ISS stage 1 disease died before receiving treatment or during 1L treatment, whereas 38% of patients with R-ISS stage 3 disease received five lines of treatment (Yong *et al*, 2016). In a recent study (Tandon *et al*, 2017), in which the R-ISS and ISS were applied to an RRMM population, almost two thirds of patients in the analysis (65%) were placed into the R-ISS Group 2. It is likely that the patients in that large group had heterogeneous disease characteristics and survival expectations; however, the R-ISS was unable to discriminate between them (Tandon *et al*, 2017). RRMM is a complex disease; therefore, several factors need to be taken into consideration to assess risk appropriately in patients at the initiation of 2L treatment. When analysed in the RMG data set, the RSA Cox model outperformed the R-ISS and ISS Cox models (data not shown; unpublished observations). The RSA covers multiple disease dimensions and, as a result, includes 16 parameters when assessing risk of death, with the exception of analysis of CA, all of which are routinely available. Tools with a narrow focus on a limited number of disease-related factors may be inaccurate when applied to complex diseases and may not provide the right patient-specific risk assessment to support therapy and management decisions. Instead, a balance of complexity and clinical practicality is required to provide a tool that will improve disease understanding and patient management.

While the R-ISS and ISS have focused on disease-related parameters, other studies have reported links between survival and frailty parameters in newly diagnosed cohorts. Real-world data from patients with MM in the Netherlands have shown that relative survival decreased significantly with age (Schaapveld *et al*, 2010). The IMWG went further and assessed the impact of frailty on survival in a pooled analysis of 869 patients with MM (Palumbo *et al*, 2015b). Each patient was assigned a frailty score based on age, comorbidities, cognitive and physical conditions, and was stratified into one of three groups (fit, intermediate fitness and frail). Three-year OS rates were significantly higher in fit patients than in intermediate fitness or frail patients (Palumbo *et al*, 2015b). Neither study considered the impact of disease aggressiveness. The RSA is the first integrated tool that allows physicians to quantify the relative impact of patient frailty and disease aggressiveness on survival outcomes in patients with MM at relapse.

Our algorithm also highlights the need to consider experiences during 1L to accurately determine the prognosis at the initiation of 2L. The influence of 1L outcomes on subsequent treatment lines was illustrated in a real-world chart audit of patients from seven European countries; this showed that experiencing an AE during a line of treatment and not achieving a VGPR or better, each significantly reduced the chances of a patient receiving the next line of treatment

(Yong *et al*, 2016). It can therefore be expected that, by preventing patients receiving the next treatment line, such experiences would also adversely affect their prognosis.

Although the higher OS values in the validation cohort may indicate a healthier population than in the development cohort, the patient characteristics do not support this conclusion. The patients in the validation cohort were treated more recently than the development cohort and therefore had the opportunity of being treated with novel agents at later treatment lines. With this exception, treatment patterns were broadly consistent across the risk groups in both the development and validation cohorts, and did not appear to be influenced by risk of patient death. This could suggest that physicians may not be able to predict patients' prognoses accurately when making treatment decisions. Alternatively, it may highlight the complexity of determining patient prognoses and optimal treatment options at 2L. Traditionally, the class of agent would only be changed when the previous line of treatment has failed. Our tool suggests that 16 factors need to be considered to determine prognosis accurately. This could be perceived as challenging in the clinic, but most parameters are either measured routinely or readily available. While CA at relapse is not routinely measured in clinical practice, and therefore not suitable for inclusion in the RSA, data suggest that there is an association between the frequency of high-risk cytogenetic lesions in patients at relapse and survival outcomes (Dimopoulos *et al*, 2015). Thus, it would be of interest in future work to measure CA at relapse and to investigate how this variable may contribute to predicting overall survival.

The RSA was developed and validated in a cohort that was treated with either proteasome inhibitors or immunomodulators initiating 1L treatment. While this is reflective of some European countries, where many patients do not receive combination therapies at 1L (Raab *et al*, 2016), it is becoming standard practice in other countries (e.g. the United States) to combine these agents at 1L (Rifkin *et al*, 2016). While current practice has started to combine these agents at 1L, robust OS data are not readily available because these patients have been treated very recently. Future work could test the RSA in a cohort of patients treated with combination therapy at 1L.

There is potential for the algorithm defined in our study to be converted into a tool to aid physicians with their patient management. In the future, this may also help with the complex treatment decisions that need to be made at first relapse. Cost constraints and the AE profiles of some double- and triplet regimens are likely to limit the extent to which the most effective regimens are used in the clinic. More research is needed to identify the optimum treatment strategy for patients in each risk group. However, through systematic assessment of risk, and the extent to which patient frailty and disease aggressiveness contribute to risk, the RSA can provide valuable information to help physicians select

the treatment regimen and dosing schedule on an individual basis.

In conclusion, we have developed and validated an algorithm that can stratify patients in routine clinical practice according to their clinical expectations. The value of this RSA lies in its ability to define patient-specific risk and combine both frailty and disease aggressiveness into a single tool that can help guide management decisions in response to the relapse of patients with MM, ultimately to improve outcomes.

### Disclosures

RH has received research funding from Amgen and Celgene, consultancy fees from Amgen, Celgene and Takeda, and honoraria from Amgen, Bristol-Myers Squibb and Janssen. MD has received research funding from Janssen and Celgene, and honoraria from Amgen, BMS, Celgene, Janssen and Takeda. MSR has received research funding from Amgen and Novartis, has received consultancy fees from Amgen, Bristol-Myers Squibb and Novartis, and has participated in advisory boards for Celgene and Janssen, and in speaker bureau for Janssen. PS is an employee of Amgen Europe and a stockholder in Amgen Inc. LD is an employee of Amgen Ltd and a stockholder in Amgen Inc. IS has received research funding from Celgene, and honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Novartis and Takeda. JR has no conflicts to disclose. LP has no conflicts to disclose. SGM is an employee of Amgen Europe and a stockholder in Amgen Inc. WB is an employee of Pharmarit International who received funding from Amgen to conduct this research.

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### Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Fig S1.** Total risk scores, frailty risk score and disease aggressiveness risk scores by group.

**Table S1.** Patient chart review demographics of the validation cohort.

**Table S2.** Characteristics of patients in each risk group of the development cohort.

**Table S3.** Treatment outcomes stratified by risk group.

**Appendix S1.** Calculation formula to measure risk score.

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