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Development of a prognostic model for overall survival in multiple myeloma using the Connect® MM Patient Registry

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Summary

Median overall survival (OS) has improved for patients with newly diagnosed multiple myeloma (NDMM), but prognosis varies depending on baseline patient characteristics. Current models use data from selected clinical trial populations, which prevent application to patients in an unselected community setting that reflects routine clinical practice. Using data from the Connect® MM Registry, a large, US, multicentre, prospective observational cohort study (Cohort 1: 2009–2011; Cohort 2: 2012–2016) of 3011 patients with NDMM, we identified prognostic variables for OS via the multivariable analysis of baseline patient characteristics in Cohort 1 (n = 1493) and developed a tool to examine individual outcomes. Factors associated with OS (n = 1450 treated patients; $P < 0{\cdot}05$) were age, del (17p), triplet therapy use, EQ-5D mobility, International Staging System stage, solitary plasmacytoma, history of diabetes, platelet count, Eastern Cooperative Oncology Group performance status and serum creatinine, which were used to create survival matrices for 3- and 5-year OS. The model was internally and externally validated using Connect MM Cohort 2 (Harrell's concordance index, 0·698), MM-015 (0·649), and the phase 3 FIRST (0·647) clinical trials. This novel prognostic tool may help inform outcomes for NDMM in the era of triplet therapy use with novel agents.

Keywords: myeloma, registry, survival, prognosis, matrix.

In 2018, approximately 30 770 patients had newly diagnosed multiple myeloma (NDMM) in the United States (Surveillance, Epidemiology, & End Results [SEER], 2019). Real-world data have shown that prognosis today is significantly better than in the past; the risk of death was 35% lower in patients with a diagnosis of NDMM in 2011–2014 *versus* those with a diagnosis in 2006–2010 (Maiese *et al*, 2018). Overall survival (OS) rates have improved since the steroid and chemotherapy era (Bergsagel, 2014) due to autologous stem cell transplantation (ASCT) (Child *et al*, 2003), novel agent use (Fonseca *et al*, 2017), optimization of triplet regimens (Durie *et al*, 2017), and maintenance therapy use in recent years (McCarthy *et al*, 2017). The gap in 2-year survival between patients with NDMM diagnosed between 2006 and 2012 and matched controls decreased at a rate of 3% per year (Fonseca *et al*, 2017). Early mortality (EM) rates (death within <1 year of diagnosis) have decreased by >5% in NDMM (Kumar *et al*, 2014).

The inclusion of novel agents, such as immunomodulatory agents and proteasome inhibitors, in triplet regimens during initial therapy for NDMM has extended median OS to >5 years within the past decade, notably by expanding triplet therapy to the elderly and by reducing EM by>5% (Kumar *et al*, 2014; Durie *et al*, 2017; Raza *et al*, 2017). The median OS increased from 4·6 years in 2005, to 6·1 years in 2010 (P = 0·002). Median OS improvements were also reported in

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patients aged >65 years (5 years [95% CI 4·1–not reached] vs. 3·2 years [95% CI 2·4–3·8]), however, no significant difference was found in patients aged <65 years (medians not reached) (Kumar *et al*, 2014). Triplet combination therapy with lenalidomide, bortezomib and dexamethasone is a standard induction therapy for NDMM regardless of transplant intent, and a median OS of 75 months was reported for non-transplant patients (Rajkumar & Kumar, 2016; Attal *et al*, 2017; Durie *et al*, 2017). Optimal triplet regimens for transplant-eligible and -ineligible patients with NDMM remain under clinical investigation (Durie *et al*, 2017; Facon *et al*, 2018; Gay *et al*, 2018).

Prognostic factors included in models for NDMM can be applied to risk stratification, individualized patient prognosis, and assist clinicians in treatment recommendations. Examples of these are baseline patient- and disease-specific characteristics, such as age, performance status (PS), high-risk cytogenetics (occurring in 25–30% of patients with NDMM), including del (17p), t(4;14), t(14;16) and chromosome 1q gain (Rajkumar & Kyle, 2005; Badros, 2010; Sonneveld *et al*, 2016), platelet count and serum creatinine (Biran *et al*, 2013a; Biran *et al*, 2013b). Conflicting data exist for other factors, possibly because of differing patient populations. Initial risk stratification systems for MM used factors solely focused on tumour burden to identify high-risk patients [(Biran *et al*, 2013a); e.g., the Durie-Salmon staging system emphasized myeloma burden, not accounting for biological variability of MM or subjectivity of assessing bone lesions on skeletal survey (Hanbali *et al*, 2017)]. The current standard for MM staging has evolved to the International Staging System (ISS; which uses β_2-microglobulin and serum albumin) and the revised ISS [R-ISS; which incorporates serum lactate dehydrogenase (LDH) and high-risk chromosomal abnormalities], which are commonly used to stratify patients and compare outcomes in clinical trials (Greipp *et al*, 2005; Biran *et al*, 2013a; Palumbo *et al*, 2015). Given its primary use in clinical trials, application of the R-ISS in daily clinical practice is limited and may not apply to typical patients receiving treatment, considering that 40% of patients with NDMM are projected to be ineligible for clinical trials (Hanbali *et al*, 2017; Shah *et al*, 2017). The R-ISS was developed using few prognostic factors and data from selected groups ($N = 3060$) enrolled in clinical trials (68% ≤65 years, 65% eligible for ASCT) (Palumbo *et al*, 2015). Furthermore, standard-of-care novel therapies and triplet combinations have shifted many "high-risk" patients to the standard-risk category, warranting the inclusion of genetics to better stratify patients (Badros, 2010; Moreau *et al*, 2016; Attal *et al*, 2017). Most knowledge of factors associated with outcomes is based on clinical trial data in which selection bias often excludes certain patients [i.e., the elderly (>70 years), those who are transplant ineligible, or those with comorbidities] (Polite *et al*, 2017), which prevent application of prognostic data to these patients. Assessing factors associated with outcomes in an unselected community setting would better reflect the heterogeneity of patients in routine clinical practice (Shah *et al*, 2017).

The Connect® MM Registry is a large, US, multicentre, prospective observational cohort study of patients with NDMM that includes > 3000 patients from 250 community, academic and government sites. By design, most enrolled patients (84%) are from community sites (Rifkin *et al*, 2015) to reflect where patients with MM are typically treated in the United States. Data from this registry were previously used to develop a model that examined EM (death ≤6 months from diagnosis) risk in patients with NDMM (Terebelo *et al*, 2017). Using data from the Connect MM Registry, we assessed factors associated with OS and used these findings to develop and validate a survival matrix to provide individualized 3- and 5-year OS based on a diverse array of patient characteristics, distinct from the generalized outcomes provided by the R-ISS.

Methods

Study design

The Connect MM Registry (NCT01081028) was designed to examine real-world diagnostic patterns, treatment patterns, clinical outcomes and health-related quality of life patient-reported outcomes in patients with NDMM (Rifkin *et al*, 2015). Eligible patients were aged ≥18 years and had symptomatic MM diagnosed within 2 months before enrolment, as defined by the International Myeloma Working Group criteria (Kyle & Rajkumar, 2009). The registry comprises 2 cohorts: Cohort 1 ($n = 1493$) includes patients enrolled from September 2009 to December 2011, and Cohort 2 ($n = 1518$) includes patients enrolled from December 2012 to April 2016. The gap in enrolments between cohorts was not planned; the decision to begin Cohort 2 enrolment was made 1 year after completion of Cohort 1 enrolment. To minimize enrolment bias, enrolment was competitive, and consecutive patients with MM presenting to the sites were evaluated for potential enrolment; the median time from diagnosis to enrolment was 25 days. Patients were treated at the clinicians' discretion and were followed up for treatment and outcomes until early discontinuation or end of study (expected 2024). All patients were required to provide written informed consent on enrolment. The Connect MM Registry was approved by a central institutional review board (IRB; Quorum Review IRB, Seattle, WA, USA) or the IRB at the individual study site. Details on the patient population and study design were previously described (Rifkin *et al*, 2015).

Analysis

Cohort 1 data were used to evaluate the association of baseline characteristics with OS; variables represented a comprehensive set of patient- and disease-related characteristics and were not pre-selected (Terebelo *et al*, 2017). A multistep analysis was conducted to compensate for missing data attributable to the noninterventional nature of registry studies (Data S1)

(Srinivasan *et al*, 2018). During the initial univariate screening for important prognostic factors, a series of univariate Cox regression models were used to identify variables significantly associated with OS in patients aged ≤75 and >75 years. Age 75 years was determined to be the most discriminating age cut-off to identify independent factors significantly associated with OS (Supplemental Figs 1 and 2, complex background equation and age distribution of registry patients). Note, 70 years was previously used as the age cut-off for elderly patients with MM in studies of EM and survival outcomes (Anagnostopoulos *et al*, 2005; Kumar *et al*, 2014).

Variable selection methods included stepwise regression (e.g. forward or backward), Lasso methods and approaches that combined theory-based variable selection with data-driven variable selection (Bendel & Afifi, 1977; Mickey & Greenland, 1989; Bursac *et al*, 2008). Each approach to model construction leads to a possibly different model specification. However, given the emphasis on the prognostic performance of the models *versus* the inference one might draw about each specific regression parameter, we determined that the resulting prognosis matrices from these candidate models did not differ qualitatively. Thus, we chose to present results for a final model that included all variables significant at $P < 0{\cdot}15$ and with <60% missing data (Table SI). While using this particular cut-off value for inclusion might lead to extraneous covariates being included in the final model, their inclusion does not alter the unbiasedness of the other prognostic variables or the unbiasedness of the estimated prognosis. Furthermore, choosing a cut-off as low as $P < 0{\cdot}05$ can lead to exclusion of important variables.

To mitigate the effect of missing data, our analyses applied multiple imputation methods to create 50 complete data sets using a fully conditional specification regression method appropriate for varying missing data patterns across multiple variables with missing values (van Buuren, 2007). In separate sensitivity analyses, we determined that the number of imputed data sets (we also assessed 25 and 100 imputed data sets; Data S1 and Table SII) did not affect the conclusions of our investigations (Graham *et al*, 2007). In addition, we ran a complete-case analysis (Data S1 and Figure S3) that also did not alter the conclusions presented here. Candidate models were selected by multivariable Cox regression using weighted observations, after stacking each of the 50 imputed data sets. For final model selection and inference combining, multivariable Cox regression was performed for each of the 50 data sets and for each candidate model (Figure S4, proportional hazards assumption plots) (Srinivasan *et al*, 2018). Selection was based on calculations of the minimum average Bayesian information criterion, and estimates were combined using Rubin's method (Rubin, 1987).

Development of prognostic chart

Based on the final model, key prognostic variables for OS were placed into charts; the larger the representative block, the greater the effect. The chart was traffic colour-coded based on the probability of survival: green indicated higher estimated probability and yellow to red, lower probabilities. Higher-risk groups were located in the bottom left corner and lower-risk groups toward the top right corner.

Internal validation

Bootstrap resampling was used to cross-validate 100 samples from the original data (baseline hazard function estimated in training and validation data sets) (Srinivasan *et al*, 2018); Harrell's C-index (Steyerberg *et al*, 2010) was used to compare the training and test bootstrap sampling. The percentage reduction in concordance probability in the test bootstrap resampling estimate compared with the training bootstrap estimate was calculated to determine whether the prognostic model was overfitted to the data. The training optimism-adjusted concordance probability of the fitted model was estimated; a probability significantly >50% indicated a good prognostic model.

External validation

External validation was performed using data from Cohort 2 of the Connect MM Registry (median follow-up = 18·3 months [range 0·2–41·9 months]) and from Celgene-sponsored randomized phase 3 trials in patients with NDMM (MM-015 [$N = 459$] and MM-020 [FIRST; Frontline Investigation of Lenalidomide + Dexamethasone *Versus* Standard Thalidomide; $N = 1623$]) (Palumbo *et al*, 2012; Benboubker *et al*, 2014; Terebelo *et al*, 2017; Srinivasan *et al*, 2018). Details of external validation, including the conversion and estimation of EQ-5D mobility scores and Eastern Cooperative Oncology Group (ECOG) PS, are presented in the Data S1. Prognostic variables for OS in external-study patients were constructed from the Cox model and compared with actual survival outcomes, after which the plot of the actual probabilities *versus* the probabilities using the models were constructed. The concordance probabilities for the models applied to the external data were evaluated using Harrell's C-index – a goodness-of-fit measure (Steyerberg *et al*, 2010).

RESULTS

Patient demographics and treatment

Overall, 1493 protocol-eligible patients who enrolled in Cohort 1 of the Connect MM Registry had adequate baseline and post-baseline data. To minimize bias, each consecutive patient at a site was screened for enrolment; 92% of screened patients were enrolled. As of 7 July 2016, data cut-off, median follow-up was 59·5 months (range 0–80·2 months), and median time from diagnosis to enrolment was 25 days. The median age of the patients was 67 years. Most patients had a

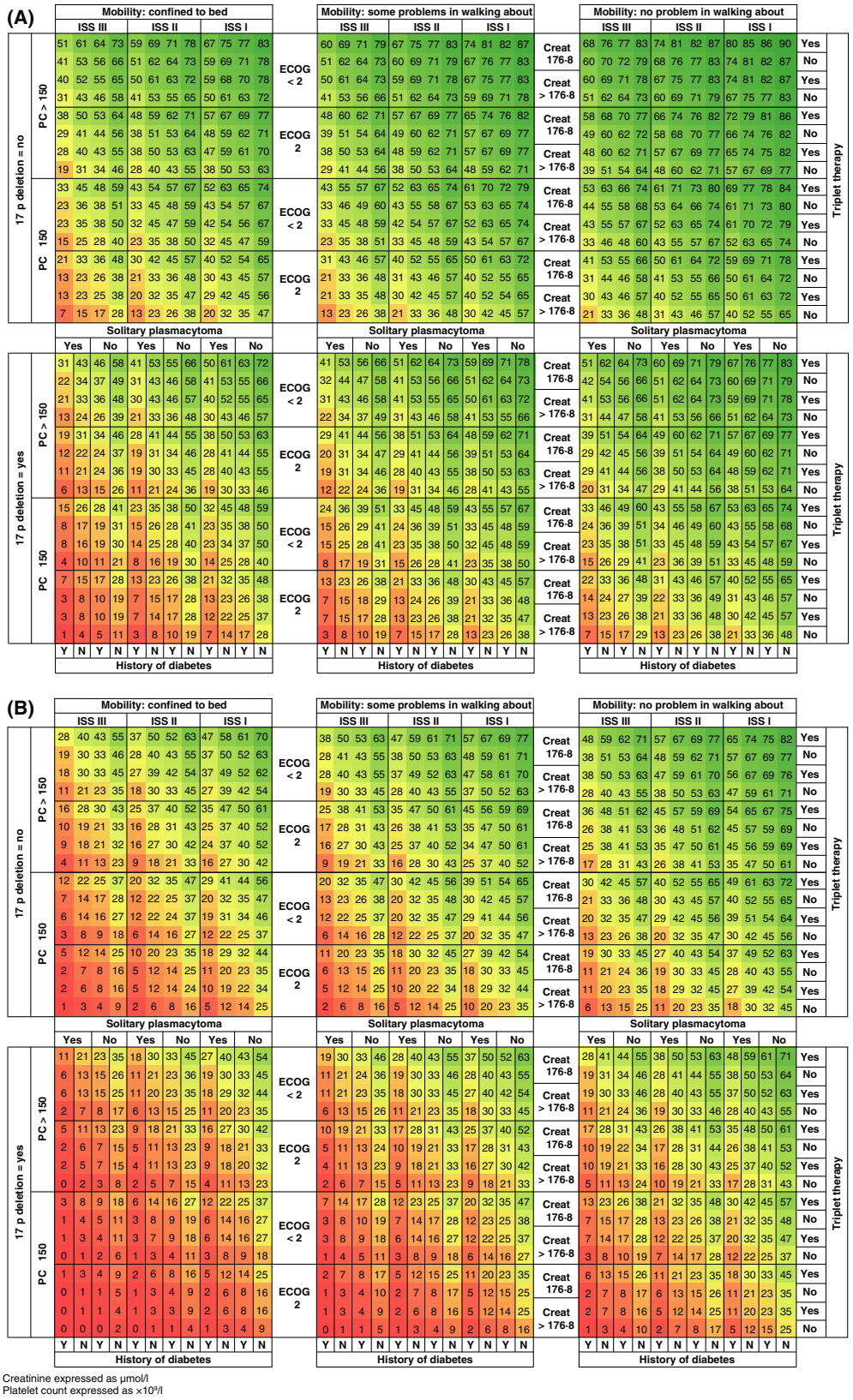

Fig 1. Three-year overall survival matrix for patients aged (A) ≤75 years and (B) >75 years. Creat, creatinine (μmol/l); ECOG, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; N, no; PC, platelet count ($\times 10^9$/l); Y, yes.

Fig 2. Five-year overall survival matrix for patients aged ≤75 years (A) and >75 years (B). Creat, creatinine (μmol/l); ECOG, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; N, no; PC, platelet count ($\times 10^9$/l); Y, yes.

history of comorbidities at baseline, including hypertension requiring treatment (56%) and diabetes (19%). Nearly 50% of patients were categorized as standard or low risk per International Myeloma Working Group criteria (Table I).

Of the enrolled patients, 1450 were treated, and the majority (81%) were treated in a community setting. The median start time of induction therapy after diagnosis was 14 days (Table SII, most common induction regimens). Most (91%) patients were treated with at least 1 novel therapy in their first drug regimen.

Overall survival

The median OS among all treated patients ($n = 1450$) was 65·7 months (Figure S5, OS curve for all enrolled patients). The 3- and 5-year OS rates were 68% and 53%, respectively. There were 636 deaths; 53% (23% of the study cohort) were directly attributed to MM disease progression (Table SIV). Besides disease progression, common causes of death were treatment-related toxicities and/or adverse events (14% of deaths, 6% of total population) and unknown causes (12% of deaths, 5% of total population); 68% of deaths were attributable to MM disease or treatment.

Cox regression analysis

In the univariate analysis, 30 baseline factors were associated with OS ($P < 0·15$; Table II). These factors were entered into a series of multivariable models, which identified 10 baseline factors associated with OS ($P < 0·05$): age, EQ-5D mobility, del (17p), ISS stage, platelet count, solitary plasmacytoma, ECOG PS, history of diabetes, creatinine category and triplet therapy use (Table II). These factors were used to create survival matrices of 3- and 5-year OS rates in patients aged ≤75 and >75 years (Figs 1 and 2). Here, we describe how a clinician may apply this information for their individual patient: first, the matrix is selected by age. Next, del(17p) status, platelet count, ECOG PS and creatinine level focus on 2 rows. Then, the answer to the mobility question and ISS stage focus on 4 columns, leaving a 2 × 4 square. Last, triplet therapy, solitary plasmacytoma, and history of diabetes select a single cell. For example, a 63-year-old patient who had a del(17p) mutation, platelet count of 135 × 10^9/l, ECOG PS of 1, and serum creatinine of 327 μmol/l would be in rows 5–6 from the bottom. Then, answering 'no problem in walking about' to the EQ-5D mobility question and ISS stage I disease focus on the 4 right columns of the matrix. Finally, treatment with triplet therapy, solitary plasmacytoma, and history of diabetes identify a single cell: 43% chance of living >3 years (Fig 1A) and a 22% chance of living >5 years (Fig 2A) after diagnosis.

Validation

For internal cross-validation, a 0·67% reduction was found for the concordance probability in the test bootstrap resampling estimate *versus* the training bootstrap estimate. The training optimism-adjusted concordance probability of the fitted Cox model was estimated as 69·5% (95% CI 66·8–72·3%). Harrell's C-index results were robust and consistent in external validations for 3-year results, thus confirming the validity of the model (Fig 3). The concordance probabilities for external validations using NDMM patient data from Cohort 2 of the Connect MM Registry, MM-015 phase 3 trial and MM-020 (FIRST) trial were 69·8%, 64·9% and 64·7%, respectively. The follow-up period in the Cohort 2 population was not long enough to validate 5-year results; however, Harrell's C-index scores for 5-year data remained the same as for the 3-year data for validation using MM-015 and MM-020 data.

Discussion

Although novel agents, ASCT and triplet therapy have contributed to longer OS in patients with NDMM (San Miguel *et al*, 2008; Warren *et al*, 2013; Roussel *et al*, 2014; Rajkumar, 2016; Attal *et al*, 2017; Durie *et al*, 2017; Kastritis *et al*, 2017), these improvements are greatly affected by baseline characteristics (Biran *et al*, 2013a; 2013b). This is the first application of a novel prognostic tool to a heterogeneous [community (81%), academic (18%) and government (1%) settings] patient population from the Connect MM Registry to identify prognostic factors for long-term survival (Rifkin *et al*, 2015) and the second application to examine outcomes and survival (Terebelo *et al*, 2017). This analysis identified patient-, disease-, quality-of-life and treatment-specific factors known to affect OS, including age, history of diabetes, mobility, del(17p), triplet therapy use and ISS stage in data from patients more representative of typical clinical settings than randomized clinical trials (Wu *et al*, 2014; Harousseau & Attal, 2017; Kastritis *et al*, 2017). This survival matrix allows for robust, individualized prognostication of long-term survival in real-world patients with NDMM, based on a variety of characteristics.

While the R-ISS is an important tool for examining long-term prognosis, it has limitations in NDMM. The score is point-based, incorporating few disease-specific prognostic markers: serum β_2-microglobulin, LDH, albumin and chromosomal abnormalities (Palumbo, *et al*, 2015). The R-ISS–based probabilities of 5-year OS are 82%, 62% and 40% for stages I, II and III disease, respectively (Palumbo *et al*, 2015). The R-ISS was validated using an independent cohort of unselected patients ($N = 475$) from a single centre: the probabilities of 5-year OS were 77%, 53% and 19%, respectively ($P < 0·001$) (Kastritis *et al*, 2017). The nearly 50% reduction in survival probability for patients with stage III in this population suggests that clinical trial selection bias imparts a higher 5-year OS in the frailest and sickest patients, who are typically excluded from clinical trials. In this multivariable analysis, the high-risk chromosomal abnormality del(17p) was the only R-ISS prognostic marker linked to longer

Table I. Baseline characteristics and treatment.

Characteristic	Death within 0 to 3 years (n = 441)	Death at > 3 years or censored (n = 1052)	Death within 0 to 5 years (n = 602)	Death at > 5 years or censored (n = 891)	All patients (N = 1493)
Patient-specific					
Age					
Median (range), years	70 (38–94)	65 (24–93)	70 (38–94)	65 (24–93)	67 (24–94)
<65 years, *n* (%)	152 (34·5)	497 (47·2)	207 (34·4)	442 (49·6)	649 (43·5)
65 to < 75 years, *n* (%)	124 (28·1)	333 (31·7)	176 (29·2)	281 (31·5)	457 (30·6)
≥75 years, *n* (%)	165 (37·4)	222 (21·1)	219 (36·4)	168 (18·9)	387 (25·9)
Male, *n* (%)	250 (56·7)	604 (57·4)	347 (57·6)	507 (56·9)	854 (57·2)
Race, *n* (%)*					
White	367 (83·2)	854 (81·2)	510 (84·7)	711 (79·8)	1221 (81·8)
Black	56 (12·7)	141 (13·4)	70 (11·6)	127 (14·3)	197 (13·2)
Median body mass index (range), kg/m^2	27·4 (13·5–55·1)	27·9 (13·5–58·7)	27·4 (13·5–55·1)	28·0 (13·5–58·7)	27·8 (13·5–58·7)
ECOG PS ≥ 2, *n* (%)	87 (19·7)	89 (8·5)	100 (16·6)	76 (8·5)	176 (11·8)
History of diabetes, *n* (%)	112 (25·4)	166 (15·8)	140 (23·3)	138 (15·5)	278 (18·6)
History of hypertension requiring treatment, *n* (%)	278 (63·0)	565 (53·7)	375 (62·3)	468 (52·5)	843 (56·5)
History of VTE, *n* (%)	25 (5·7)	40 (3·8)	33 (5·5)	32 (3·6)	65 (4·4)
del(17p), *n* (%)	44 (10·0)	66 (6·3)	59 (9·8)	51 (5·7)	110 (7·4)
t(4;14), *n* (%)	20 (4·5)	41 (3·9)	29 (4·8)	32 (3·6)	61 (4·1)
t(11;14) from FISH, *n* (%)	40 (9·1)	89 (8·5)	53 (8·8)	76 (8·5)	129 (8·6)
t(14;16) from FISH, *n* (%)	13 (2·9)	23 (2·2)	18 (3·0)	18 (2·0)	36 (2·4)
History of MGUS, *n* (%)	48 (10·9)	113 (10·7)	64 (10·6)	97 (10·9)	161 (10·8)
History of smouldering myeloma, *n* (%)	21 (4·8)	65 (6·2)	33 (5·5)	53 (5·9)	86 (5·8)
Disease-specific					
Lactate dehydrogenase, *n* (%)	36 (8·2)	75 (7·1)	45 (7·5)	66 (7·4)	111 (7·4)
History of solitary plasmacytoma, *n* (%)	63 (14·3)	121 (11·5)	82 (13·6)	102 (11·4)	184 (12·3)
Extramedullary plasmacytoma, *n* (%)	30 (6·8)	39 (3·7)	38 (6·3)	31 (3·5)	69 (4·6)
Immunoglobulin G class (≥50 vs. <50 g/l), *n* (%)	242 (54·9)	636 (60·5)	330 (54·8)	548 (61·5)	878 (58·8)
Albumin < 35 g/l, *n* (%)	219 (49·7)	424 (40·3)	292 (48·5)	351 (39·4)	643 (43·1)
Calculated ISS stage, *n* (%)					
I	56 (12·7)	278 (26·4)	82 (13·6)	252 (28·3)	334 (22·4)
II	102 (23·1)	277 (26·3)	152 (25·2)	227 (25·5)	379 (25·4)
III	174 (39·5)	251 (23·9)	223 (37·0)	202 (22·7)	425 (28·5)
Myeloma bone involvement, *n* (%)†	331 (75·1)	812 (77·2)	459 (76·2)	684 (76·8)	1143 (76·6)
Hypercalcemia (serum calcium ≥ 2·875 mmol/l), *n* (%)	45 (10·2)	63 (6·0)	57 (9·5)	51 (5·7)	108 (7·2)
Renal insufficiency (serum creatinine> 176·8 μmol/l), *n* (%)	117 (26·5)	154 (14·6)	141 (23·4)	130 (14·6)	271 (18·2)
Anaemia (haemoglobin < 100 g/l or> 2 below LLN), *n* (%)	238 (54·0)	430 (40·9)	309 (51·3)	359 (40·3)	668 (44·7)
Median platelet count (range), x10^9/l‡	192 (24–787)	220 (10–1540)	195 (24–787)	222 (10–1540)	211 (10–1540)
IMWG risk category, *n* (%)					
High	83 (18·8)	170 (16·2)	117 (19·4)	136 (15·3)	253 (16·9)
Standard	162 (36·7)	433 (41·2)	230 (38·2)	365 (41·0)	595 (39·9)
Low	15 (3·4)	75 (7·1)	20 (3·3)	70 (7·9)	90 (6·0)
β_2-Microglobulin ≥ 5·5 mg/l, *n* (%)	166 (37·6)	245 (23·3)	214 (35·5)	197 (22·1)	411 (27·5)
Clonal bone marrow plasma cells ≥ 10%, *n* (%)	376 (85·3)	906 (86·1)	520 (86·4)	762 (85·5)	1282 (85·9)
Serum monoclonal protein ≥ 30 g/l, *n* (%)	103 (23·4)	250 (23·8)	143 (23·8)	210 (23·6)	353 (23·6)
Serum free light-chain abnormality, *n* (%)*	88 (20·0)	176 (16·7)	111 (18·4)	153 (17·2)	264 (17·7)

Table I. (*Continued*)

Characteristic	Death within 0 to 3 years (n = 441)	Death at > 3 years or censored (n = 1052)	Death within 0 to 5 years (n = 602)	Death at > 5 years or censored (n = 891)	All patients (N = 1493)
Pathological fracture, n (%)	170 (38·5)	405 (38·5)	232 (38·5)	343 (38·5)	575 (38·5)
HRQoL from EQ-5D, n (%)					
Self-care from EQ-5D					
1	242 (54·9)	715 (68·0)	355 (59·0)	602 (67·6)	957 (64·1)
2	123 (27·9)	201 (19·1)	153 (25·4)	171 (19·2)	324 (21·7)
3	12 (2·7)	12 (1·1)	13 (2·2)	11 (1·2)	24 (1·6)
Mobility from EQ-5D					
1	116 (26·3)	446 (42·4)	176 (29·2)	386 (43·3)	562 (37·6)
2	257 (58·3)	477 (45·3)	339 (56·3)	395 (44·3)	734 (49·2)
3	6 (1·4)	6 (0·6)	8 (1·3)	4 (0·4)	12 (0·8)
Novel therapy					
Use of novel agents in first regimen, n (%)					
0	45 (10·2)	93 (8·8)	63 (10·5)	75 (8·4)	138 (9·2)
1	311 (70·5)	647 (61·5)	416 (69·1)	542 (60·8)	958 (64·2)
≥2	85 (19·3)	312 (29·7)	123 (20·4)	274 (30·8)	397 (26·6)
Triplet treatment, n (%)	161 (36·5)	488 (46·4)	229 (38·0)	420 (47·1)	649 (43·5)
Immunomodulatory agent–containing therapy use, n (%)	207 (46·9)	561 (53·3)	282 (46·8)	486 (54·5)	768 (51·4)
PI-containing therapy use, n (%)	302 (68·5)	762 (72·4)	419 (69·6)	645 (72·4)	1064 (71·3)
Treatment setting, n (%)					
Community	358 (81·2)	853 (81·1)	495 (82·2)	716 (80·4)	1211 (81·1)
Academic	76 (17·2)	187 (17·8)	100 (16·6)	163 (18·3)	263 (17·6)
Government	7 (1·6)	12 (1·1)	7 (1·2)	12 (1·3)	19 (1·3)

ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; HRQoL, health-related quality of life; IMWG, International Myeloma Working Group; ISS, International Staging System; LLN, lower limit of normal; MGUS, monoclonal gammopathy of undetermined significance; PI, proteasome inhibitor; VTE, venous thromboembolism.

*Also included race not specified (n = 43), other (n = 19), Asian (n = 6), American Indian/Alaskan Native (n = 3), Pacific Islander (n = 3), and data not provided (n = 1); 91 patients were of Hispanic or Latino ethnicity.

†See the Data S1 for details on the derivation of bone involvement criteria and serum free light-chain abnormality.

‡n = 412 (death within 0–3 years), n = 956 (death at> 3 years or censored), n = 566 (death within 0–5 years), n = 802 (death at> 5 years or censored), n = 1368 (all patients).

survival; however, interestingly, analysis of the R-ISS population found that age >65 years was significantly associated with poorer OS (Palumbo *et al*, 2015). Our survival matrix expands on the R-ISS by including more variables that are fully crossed (R-ISS was developed using recursive partitioning, which does not fully evaluate all possible profiles), whereas the R-ISS evaluates far fewer combinations of variables (3 ISS stages vs. standard-/high-risk chromosomal abnormalities vs. normal/high LDH) (Palumbo *et al*, 2015).

This analysis identified variables outside of R-ISS prognostic markers in a largely community-based population. The resulting matrices were validated against Cohort 2 of the Connect MM Registry and 2 clinical trial populations. In this matrix, the strongest prognostic variable for longer survival was age, which is absent from R-ISS criteria. Like R-ISS, chromosomal abnormalities, e.g. del(17p), were identified as a strong prognostic variable for survival in multivariable analyses, but the next strongest were factors not considered by R-ISS criteria: triplet therapy use, EQ-5D mobility, history of diabetes and solitary plasmacytoma. Because triplet therapy is currently a standard of care in patients with NDMM (Rajkumar & Kumar, 2016), the R-ISS is more limited in determining prognosis today than when novel agents were first introduced. These results, though from an observational registry, confirm the survival benefit of lack of comorbidities in MM (Wu *et al*, 2014) and support benefits observed with triplet therapy (Durie *et al*, 2017).

Transplant intent was not a determinant for this survival matrix. This may be explained by observed differences when comparing rates of transplant intent and actual transplant in the Connect MM Registry: 77% of patients with transplant intent who died after 3 or 5 years (or were censored) underwent ASCT, while 9% and 10% of patients with no transplant intent who died after 3 and 5 years (or were censored) underwent ASCT. Notably, in Cohort 1 of the Connect MM Registry, the ratio of transplant-eligible *versus* transplant-ineligible patients was more balanced (44% vs. 56%) than that in the R-ISS population (65% vs. 35%) (Palumbo *et al*, 2015; Kastritis *et al*, 2017).

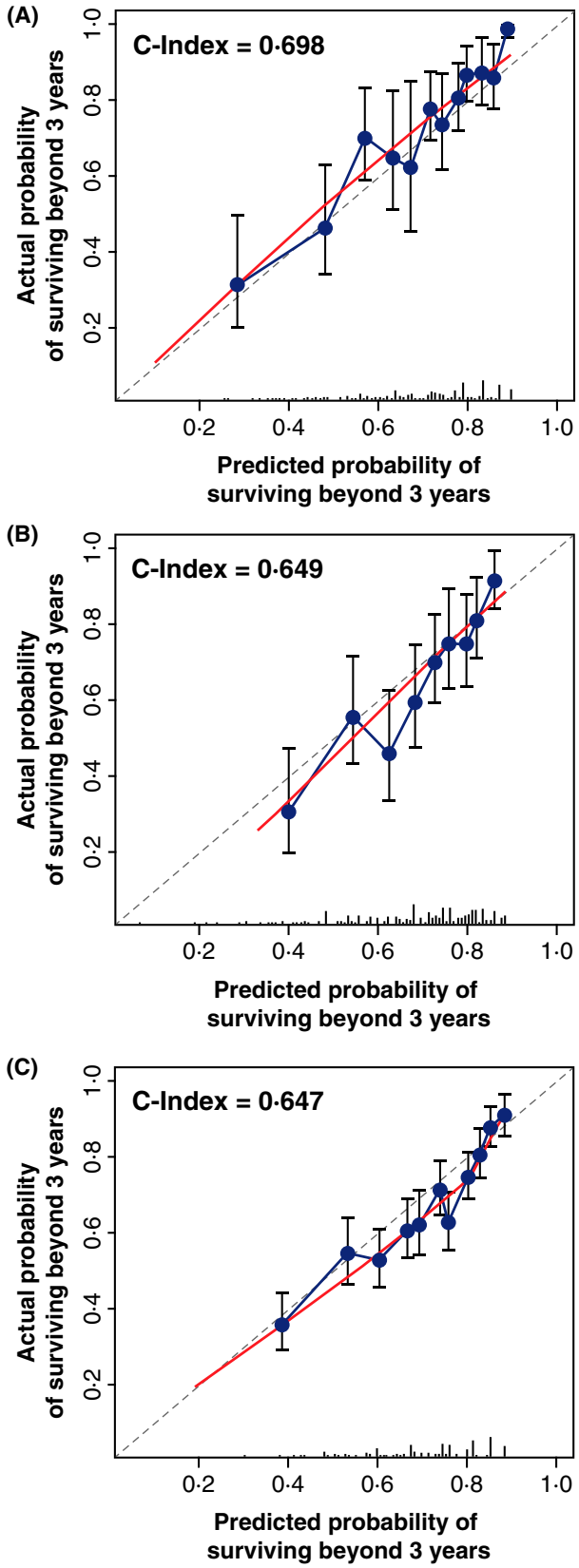

Fig 3. External validation models graphing actual *versus* estimated probabilities against (A) Connect MM Cohort 2, (B) MM-015 and (C) MM-020/FIRST data. The filled circles represent observations in groups (ordered from most probable to least probable) for whom the actual probabilities (from Cohort 2, MM-015 or FIRST trial data) are plotted against the estimated probabilities (based on the Connect MM Cox model). The dotted line and the curved solid line (nonparametric curve) are the fitted curves for the plot of actual and estimated probabilities. Harrell's concordance index (concordance probability; C-Index) is the probability that a randomly selected pair of patients in the independent external data set (1 with a poorer survival outcome than the other) will be correctly differentially identified based on entering the baseline characteristics of the 2 patients in the fitted model (Steyerberg et al, 2010).

Six of the prognostic variables for OS identified in the multivariable analysis were included in 7 previously identified for EM in the Connect MM Registry. However, differences between variables for OS and EM were observed: age was the strongest variable for OS, whereas EQ-5D mobility and ECOG PS were the strongest variables for EM.

Well-known limitations of real-world studies, such as those using patient registries, should be acknowledged, e.g. inclusion of patients not randomized to treatment, the lack of protocol-mandated specific treatments (investigator selection), formal response assessment criteria, limitations in the collection of adverse event data (only low-grade events and data most relevant to this elderly patient population), and variations in treatment duration and intensity. We also recognize, as in any observational study, the potential for missing or erroneous data (due to limited monitoring of individual sites for verification of data) to affect these types of models. However, a strength of this registry is the ability to query sites for more information on questionable data. Furthermore, by applying multiple imputation methods (see Data S1 for additional details) in the analyses (Srinivasan *et al*, 2018), the impact of missingness may also be mitigated. Despite these limitations, the Connect MM Registry allows examination of clinical outcomes in patients with NDMM treated in a mostly community-based setting, which better reflects real-world populations and clinical practice than do clinical trials. We also controlled for bias in a previously published analysis of the Registry where use of triplet therapy in second line was significantly associated with prolonged progression-free survival (Jagannath *et al*, 2018).

Prognostic scoring systems use various factors to separate large heterogeneous populations into smaller risk groups, with more distinct and predictable outcomes contributing to our understanding of MM, and help identify patients likely (or less likely) to benefit from therapy (Halabi & Owzar, 2010; Hanbali *et al*, 2017). Using the Connect MM Registry,

Table II. Baseline characteristics associated with overall survival.

Characteristic	Univariate analysis	
	HR (95% CI)	*P* value*
Patient –specific		
Age (>75 vs. ≤75 years)	2·24 (1·89–2·65)	**<0·001**
Age (>70 vs. ≤70 years)	1·88 (1·61–2·20)	**<0·001**
Body mass index, kg/m^2	0·91 (0·83–0·99)	**0·024**
ECOG performance status score (2–5 vs. 0–1)	2·12 (1·70–2·66)	**<0·001**
History of diabetes	1·61 (1·34–1·94)	**<0·001**
History of hypertension	1·37 (1·16–1·62)	**<0·001**
History of VTE	1·49 (1·06–2·08)	**0·021**
del(17p) from FISH and cytogenetic tests	1·96 (1·49–2·57)	**<0·001**
t(4;14) from FISH and cytogenetic tests	1·71 (1·19–2·48)	**0·004**
t(11;14) from FISH	1·28 (0·96–1·72)	**0·092**
t(14;16) from FISH	1·78 (1·10–2·89)	**0·019**
History of MGUS	1·02 (0·79–1·31)	0·903
History of smouldering myeloma	0·90 (0·64–1·27)	0·562
Disease-specific		
Lactate dehydrogenase (>300 vs. ≤300 iu/l)	0·99 (0·72–1·36)	0·957
History of solitary plasmacytoma	1·25 (1·00–1·57)	**0·052**
Extramedullary plasmacytoma	1·51 (1·15–2·00)	**0·003**
Immunoglobulin G class (≥50 vs. <50 g/l)	0·80 (0·66–0·98)	**0·027**
Albumin (<35 vs. ≥35 g/l)	1·48 (1·25–1·74)	**<0·001**
ISS disease stage (calculated)	1·68 (1·49–1·88)	**<0·001**
Myeloma bone involvement	0·93 (0·77–1·12)	0·429
Hypercalcemia (serum calcium ≥ 2·875 mmol/l)	1·61 (1·23–2·09)	**<0·001**
Renal insufficiency (serum creatinine> 176·8 μmol/l)	1·69 (1·41–2·03)	**<0·001**
Anaemia (hemoglobin < 100 g/l or 2 below LLN)	1·43 (1·22–1·67)	**<0·001**
Platelet count (≤150 × 10^9/l vs. >150 × 10^9/l)	1·87 (1·56–2·24)	**<0·001**
IMWG risk (high vs. standard)	1·44 (1·17–1·79)	**0·001**
β_2-Microglobulin ≥ 5·5 mg/l	2·00 (1·67–2·41)	**<0·001**
Clonal bone marrow plasma cells (≥10% vs. <10%)	1·37 (0·99–1·89)	**0·058**
Serum monoclonal protein (≥30 vs. <30 g/l)	1·07 (0·88–1·29)	0·509
Serum free light-chain abnormality	1·46 (1·02–2·08)	**0·038**
Pathological fracture	1·01 (0·86–1·19)	0·891
HRQoL from EQ-5D		
Self-care from EQ-5D	1·47 (1·25–1·72)	**<0·001**
Mobility from EQ-5D	1·69 (1·43–2·00)	**<0·001**
Novel therapy in first regimen		
Novel therapy use (0–1 vs. ≥2)	0·62 (0·51–0·75)	**<0·001**
Triplet therapy use	0·69 (0·59–0·81)	**<0·001**
Immunomodulatory agent –containing therapy use	0·75 (0·65–0·88)	**<0·001**
PI-containing therapy use	0·84 (0·71–0·99)	**0·036**

	Multivariable analysis	
	HR (95% CI)	*P* value
Patient-specific		
Age (>75 vs. ≤75 years)	1·89 (1·58–2·26)	<0·001
ECOG performance status score (2–5 vs. 0–1)	1·41 (1·05–1·88)	0·022
History of diabetes	1·40 (1·15–1·71)	0·001
del(17p) from FISH and cytogenetic forms	1·72 (1·28–2·31)	0·001
Disease specific		
History of solitary plasmacytoma	1·52 (1·21–1·91)	<0·001
ISS disease stage (calculated)	1·31 (1·14–1·49)	<0·001
Renal insufficiency (serum creatinine> 176·8 μmol/l)	1·33 (1·08–1·64)	0·008
Platelet count (≤150 × 10^9/l vs. >150 × 10^9/l)	1·64 (1·32–2·03)	<0·001
HRQoL from EQ-5D		
Mobility from EQ-5D	1·32 (1·10–1·59)	0·003
Novel therapy		
Triplet therapy use	0·77 (0·65–0·91)	0·002

CI, cmoonfidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; FISH, fluorescence in situ hybridization; HR, hazard ratio; HRQoL, health-related quality of life; IMWG, International Myeloma Working Group; ISS, International Staging System; LLN, lower limit of normal; MGUS, monoclonal gammopathy of undetermined significance; PI, protease inhibitor; VTE, venous thromboembolism.

*Boldface *P* values were used in the initial multivariable model before variable selection. All 2-factor interactions were assessed in the multivariable model. (Srinivasan *et al* 2018) These were typically of moderate effect and not clinically interpretable; thus, they were not used in the final model.

which includes data from >3000 patients from typical clinical settings, we have developed a simple and hypothesis-driven prognostic model that allows for reliable, individualized

examination of potential survival in patients with NDMM characterized by baseline data that are accessible and reproducible to the treating physician (Henry, 2008). A potential application of this matrix is to identify patients with poor prognosis (e.g. estimated 3-year OS: 30–40%) who might benefit from clinical trial interventions for which they might not routinely qualify (Shah *et al*, 2017); outcomes could be judged relative to estimated OS. This is especially pertinent in the era of triplet therapy, which has improved prognosis for patients irrespective of risk profile (Jakubowiak *et al*, 2012; Moreau *et al*, 2016; Attal *et al*, 2017). Overall, this model will help the clinician to assess patients more comprehensively when determining treatment plans and goals of therapy.

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Conflicts of interest

This study was funded by Celgene Corporation. HRT provided consultancy services to Celgene and participated in speakers' bureaus for Janssen, Takeda and Pharmacyclics LLC, an AbbVie Company. RA is a member of steering committees for Celgene and Takeda, has received research funding from Celgene and Takeda, and has received research funding from Prothena. CJG has received honoraria from Janssen, Bristol-Myers Squibb, Celgene and Takeda; provided consultancy services to Janssen, Bristol-Myers Squibb and Celgene; received travel reimbursement from Janssen, Bristol-Myers Squibb and Celgene; and received research funding from Celgene. KT provided consultancy services to Celgene, participated in speakers' bureaus for Myriad Genetics, and received travel reimbursement from Dava Oncology. BGMD provided consultancy services to Takeda and Janssen. JWH provided consultancy services to Celgene. SJ provided consultancy services to Celgene, Bristol-Myers Squibb, Novartis and Merck, and participated in speakers' bureaus for MMRF and Medicom. LW provided consultancy services to EveryFit, Gilead and Janssen. MN provided consultancy services and participated in speakers' bureaus for Celgene and participated in speakers' bureaus for Janssen. EDF, SS, LY, AK and AA are employed by Celgene. RMR provided consultancy services to Amgen, Boehringer Ingelheim, Celgene, EMD Serono, Sandoz and Takeda, and owns stocks with McKesson.

Supporting Information

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

Data S1. Methods.

Figure S1. Complex background equation relating survival to a string of prognostic variables from Cox regression.

Figure S2. Histogram of age distribution for patients with multiple myeloma.

Figure S3. Validation using observations with complete-cases for 10 variables.

Figure S4. Double log plots of survival functions versus overall survival time for covariates.

Figure S5. Overall survival curve for all patients in cohort 1 of the Connect MM Registry.

Table SI. Missing data for analytic variables in univariate analysis.

Table SII. Sensitivity analysis of baseline characteristics associated with overall survival per numbers of imputations.

Table SIII. Top 10 first-line first induction combination therapies.

Table SIV. Causes of death.

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