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 < 0.05) 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...
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 standard for MM staging has evolved to the International 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 β₂-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).
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 39.5 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
| A | Mobility: confined to bed | Mobility: some problems in walking about | Mobility: no problem in walking about | ISS I | ISS II | ISS III | ISS I | ISS II | ISS III | ISS I | ISS II | ISS III | ISS I | ISS II | ISS III | ISS I | ISS II | ISS III | ISS I | ISS II | ISS III |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| (B) | Mobility: confined to bed | Mobility: some problems in walking about | Mobility: no problem in walking about | ISS I | ISS II | ISS III | ISS I | ISS II | ISS III | ISS I | ISS II | ISS III | ISS I | ISS II | ISS III | ISS I | ISS II | ISS III | ISS I | ISS II | ISS III |
| Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Creatinine expressed as µmol/l; ECOG, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; N, no; PC, platelet count (×10^11); Y, yes. |

Fig 1. Three-year overall survival matrix for patients aged (A) ≤75 years and (B) >75 years. Creatinine (µmol/l); ECOG, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; N, no; PC, platelet count (×10^11); Y, yes.
Table 1: Patient characteristics according to 17p deletion status

| 17p deletion | Yes | No |
|--------------|-----|----|
| Age (years)  | 60-64 | 55-59 |
| Sex (male/female) | 10/10 | 15/15 |
| ECOG Performance Status | 2/0 | 1/1 |
| ISS Stage | 1/2 | 3/3 |
| Serum Creatinine (µmol/l) | 14/15 | 20/21 |

ECOG: Eastern Cooperative Oncology Group; ISS: International Staging System; PC: patient count; >: greater than.
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 $\leq 75$ 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 $2 \times 4$ 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 $135 \times 10^9/l$, ECOG PS of 1, and serum creatinine of $327 \mu mol/l$ 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 $\beta_2$-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 unscreened 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 variable 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                  |                                     |                                           |                                     |                                          |                         |
| <65 years, n (%)                       | 70 (38–94)                          | 65 (24–93)                                | 70 (38–94)                          | 65 (24–93)                               | 67 (24–94)              |
| 65 to < 75 years, n (%)                | 152 (34-5)                          | 497 (47-2)                                | 207 (34-4)                          | 442 (49-6)                               | 649 (43-5)              |
| ≥75 years, n (%)                       | 124 (28-1)                          | 333 (31-7)                                | 176 (29-2)                          | 281 (31-5)                               | 457 (30-6)              |
| Male, n (%)                            | 165 (37-4)                          | 222 (21-1)                                | 219 (36-4)                          | 168 (18-9)                               | 387 (25-9)              |
| Race                                    | 250 (56-7)                          | 604 (57-4)                                | 347 (57-6)                          | 507 (56-9)                               | 854 (57-2)              |
| White, n (%)                           | 367 (83-2)                          | 854 (81-2)                                | 510 (84-7)                          | 711 (79-8)                               | 1221 (81-8)             |
| Black, n (%)                           | 56 (12-7)                           | 141 (13-4)                                | 70 (11-6)                           | 127 (14-3)                               | 197 (13-2)              |
| Median body mass index (range), kg/m²  | 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      | 278 (63-0)                          | 565 (53-7)                                | 375 (62-3)                          | 468 (52-5)                               | 843 (56-5)              |
| treatment, n (%)                       | 25 (5-7)                            | 40 (3-8)                                  | 33 (5-5)                            | 32 (3-6)                                 | 64 (4-4)                |
| History of VTE, n (%)                  | 44 (10-0)                           | 66 (6-3)                                  | 59 (9-8)                            | 51 (5-7)                                 | 110 (7-4)               |
| del(17p), n (%)                        | 20 (4-5)                            | 41 (3-9)                                  | 29 (4-8)                            | 32 (3-6)                                 | 61 (4-1)                |
| t(4;14), n (%)                         | 40 (9-1)                            | 89 (8-5)                                  | 53 (8-8)                            | 76 (8-5)                                 | 129 (8-6)               |
| t(11;14) 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 (%)            | 56 (12-7)                           | 278 (26-4)                                | 82 (13-6)                           | 252 (28-3)                               | 334 (22-4)              |
| I                                      | 102 (23-1)                          | 277 (26-3)                                | 152 (25-2)                          | 227 (25-5)                               | 379 (25-4)              |
| II                                     | 174 (39-5)                          | 251 (23-9)                                | 223 (37-0)                          | 202 (22-7)                               | 425 (28-5)              |
| III                                    | 331 (75-1)                          | 812 (77-2)                                | 459 (76-2)                          | 684 (76-8)                               | 1143 (76-6)             |
| Myeloma bone involvement, n (%)†      | 45 (10-2)                           | 63 (6-0)                                  | 57 (9-5)                            | 51 (5-7)                                 | 108 (7-2)               |
| Hypercalcemia (serum calcium ≥ 2.875 mmol/l), n (%) | 117 (26-5) | 154 (14-6)                                | 141 (23-4)                          | 130 (14-6)                               | 271 (18-2)              |
| Renal insufficiency (serum creatinine> 176-8 μmol/l), n (%) | 238 (54-0) | 430 (40-9)                                | 309 (51-3)                          | 359 (40-3)                               | 668 (44-7)              |
| Anaemia (haemoglobin < 100 g/l or> 2 below LLN), n (%) | 192 (24–787) | 220 (10–1540) | 195 (24–787) | 222 (10–1540) | 211 (10–1540) |
| Median platelet count (range), x10⁹/l‡ | 83 (18-8) | 170 (16-2) | 117 (19-4) | 136 (15-3) | 253 (16-9) |
| IMWG risk category, n (%)              | 162 (36-7)                          | 433 (41-2)                                | 230 (38-2)                          | 365 (41-0)                               | 595 (39-9)              |
| High                                   | 15 (3-4)                            | 75 (7-1)                                  | 20 (3-3)                            | 70 (7-9)                                 | 90 (6-0)                |
| Standard                               | 166 (37-6)                          | 245 (23-3)                                | 214 (35-5)                          | 197 (22-1)                               | 411 (27-5)              |
| Low                                    | 376 (85-3)                          | 906 (86-1)                                | 520 (86-4)                          | 762 (85-5)                               | 1282 (85-9)             |
| Clonal bone marrow plasma cells ≥ 10%, n (%) | 103 (23-4) | 250 (23-8) | 143 (23-8) | 210 (23-6) | 353 (23-6) |
| Serum monoclonal protein ≥ 30 g/l, n (%) | 88 (20-0) | 176 (16-7) | 111 (18-4) | 153 (17-2) | 264 (17-7) |
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 or 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).

| 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 (%) | 1 | 242 (54-9) | 715 (68-0) | 355 (59-0) | 602 (67-6) | 957 (64-1) |
| Self-care from EQ-5D | 1 | 123 (27-9) | 201 (19-1) | 153 (25-4) | 171 (19-2) | 324 (21-7) |
| 2 | 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 (%) | 1 | 45 (10-2) | 93 (8-8) | 63 (10-5) | 75 (8-4) | 138 (9-2) |
| 0 | 311 (70-5) | 647 (61-5) | 416 (69-1) | 542 (60-8) | 958 (64-2) |
| 1 | 85 (19-3) | 312 (29-7) | 123 (20-4) | 274 (30-8) | 397 (26-6) |
| 2 | 161 (36-5) | 488 (46-4) | 229 (38-0) | 420 (47-1) | 649 (43-5) |
| 3 | 207 (46-9) | 561 (53-3) | 282 (46-8) | 486 (54-5) | 768 (51-4) |
| Immunomodulatory agent–containing therapy use, n (%) | 302 (68-5) | 762 (72-4) | 419 (69-6) | 645 (72-4) | 1064 (71-3) |
| PI-containing therapy use, 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 SI 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).
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 | 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/m² | 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 μmol/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 × 10⁹/l vs. >150 × 10⁹/l) | 1.87 (1.56–2.24) | <0.001   |
| IMWG risk (high vs. standard) | 1.44 (1.17–1.79) | 0.001    |
| β₂-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 (≥50 vs. <50 g/l) | 1.07 (0.88–1.29) | 0.509    |
| Serum free light-chain abnormality | 1.46 (1.02–2.08) | 0.038    |

### Table II. (Continued)

| Characteristic | Univariate analysis | P value* |
|----------------|---------------------|----------|
| **Pathological fracture** |                      |          |
| HRQoL from EQ-5D | 1.01 (0.86–1.19) | 0.891    |
| 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

| Characteristic | Univariate analysis | 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 × 10⁹/l vs. >150 × 10⁹/l) | 1.64 (1.32–2.03) | <0.001   |
| HRQoL from EQ-5D | 1.32 (1.10–1.59) | 0.003    |
| Mobility from EQ-5D | 0.77 (0.65–0.91) | 0.002    |

CI, confidence 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 S1. 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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