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# Development of a risk stratification algorithm in triple-class exposed and double-class exposed relapsed/refractory multiple myeloma using the Flatiron Health database

Michel Delforge,[1*] Karthik Ramasamy,[2*] Clyde Caisip,[3] Shannon Cope,[3] Devender Dhanda,[4] Thomas Debray,[5] Yu-Hsuan Shih,[4] Walter Bouwmeester[6]

[1]University Hospital Leuven, Leuven, Belgium; [2]Oxford University Hospitals NHS Trust, Oxford, UK; [3]Precision AQ, Vancouver, BC, Canada; [4]Bristol Myers Squibb, Princeton, NJ, USA; [5]Smart Data Analysis and Statistics, Utrecht, Netherlands; [6]Precision AQ, Rotterdam, Netherlands

*These authors contributed equally to this work

## Introduction

- Multiple myeloma (MM) is the second most frequent adult hematologic malignancy worldwide, and while treatment advances have improved disease outcomes nearly all patients with MM will eventually relapse[1,2]
- Risk stratification systems provide insight on how baseline risk differs across patients to inform treatment decisions
  - The International Staging System (ISS), the Revised ISS (R-ISS), and the new additive scoring system (R2-ISS) were developed to assess risk and prognosis of newly diagnosed MM and have been widely adopted in clinical practice as well as in clinical trials[3-5]
  - Existing algorithms by Hájek et al.[1] for patients with relapsed/refractory (RRMM) were based on patients in the second-line setting, and may not be applicable to double-class exposed (DCE) or triple-class exposed (TCE) patients, given differences in potential prognostic factors

## Objectives

- To identify independent predictors of overall survival (OS) and develop a risk stratification algorithm (RSA) for patients with DCE and TCE RRMM using the Flatiron Health database, which collects real-world clinical data from electronic health records (EHRs)
- To validate the RSA for progression-free survival (PFS) by generating Kaplan-Meier curves

## Methods

### Study design

- This retrospective analysis used patient-level EHRs from a nationwide USA research database (Flatiron Health)
  - The de-identified data were from structured and unstructured data curated via technology-enabled chart abstraction from physician notes and other documents originating from approximately 280 cancer clinics in the USA
  - In the MM cohort, 71% of patients were from community sites, 23% were from academic sites, and the remaining 6% were from both academic and community sites
- Study observation period: January 1, 2011, to April 29, 2024
- Study population: patients with RRMM
  - ≥ 18 years of age
  - No prior exposure to investigational drugs, elotuzumab, chimeric antigen receptor (CAR) T cell therapies, or recently approved drugs (ie, belantamab mafodotin, selinexor, elranatamab, talquetamab, and teclistamab)
  - Data available after the index date (eg, no patient deaths or loss to follow-up)
- Two distinct cohorts were developed:
  - DCE cohort: patients with RRMM and prior exposure to any 2 treatment classes, including an immunomodulatory drug (IMiD®) agent, proteasome inhibitor, and anti-CD38 monoclonal antibody
  - TCE cohort: patients with RRMM and prior exposure to all 3 treatment classes named above
- Index date: end date of the earliest line of therapy in which the patient has been exposed to 2 (DCE cohort) or 3 (TCE cohort) treatment classes
- Follow-up period: from index date to the end of study observation period or death, whichever occurred first

### Prognostic factors and outcomes

- Twenty-seven potential prognostic factors of OS in patients with DCE/TCE RRMM were identified by literature review[1,6-8] and ranked by 2 clinical experts based on importance (**Table 1**)
  - The most important prognostic factors according to the averaged clinical expert ranking include refractory status, cytogenetic risk profile, ISS/R-ISS disease stage, age, extramedullary disease, time to progression on last regimen, number of prior lines of therapy, and TSD
- Clinical outcomes included OS and PFS
  - OS was defined as time from index to death due to any cause
  - PFS was defined as time from index to end date of index line of therapy, disease progression, or death (whichever occurred first)[9]

### Statistical analysis

- Fractional polynomials were used to explore the shape of continuous predictor-OS associations in Cox proportional hazard models
  - Predictors that showed a non-linear association with OS were transformed based on clinically established cut-offs
- Multiple imputation by chained equation (MICE) was performed (N = 100) to address missing values[10,11]
- Cox proportional hazard models and augmented backward elimination (ABE) were used for variable selection[12]
  - Variables were monitored for collinearity; only the version of each correlated variable that exhibited the strongest predictor effect was retained
  - Candidate prognostic factors with high rank that were available in the Flatiron database (**Table 1**) were included in the model, independent of statistical significance
  - Variable selection was applied separately in each imputed dataset; variables that were selected by ABE in ≥ 80% of the imputed datasets were included in the RSA
  - Immunoglobulins (ie, IgA, IgG, IgM) and best response to last treatment were excluded due to a high percentage (> 40%) of missing values and lower ranking (**Table 1**)
- Cox proportional hazard models were estimated with the selected prognostic factors in each imputed dataset, and the estimated log hazard ratios were pooled using Rubin's rules[13]
- Risk scores for each patient were calculated by multiplying the log hazard ratios and corresponding patient-specific predictor value
  - Four risk groups were defined based on quartiles of the distribution of the risk score, and OS Kaplan-Meier curves were generated for each risk group
- A simplified RSA intended for clinical practice was developed based on R-ISS, age, TSD, and refractory status
- Kaplan-Meier curves for PFS were plotted per risk group to assess the performance of the RSA for predicting PFS

**Table 1. Prognostic factor selection**

| Characteristics | R-ISS | Hájek et al. RSA[1] | Average rank by clinical expert | RSA TCE comprehensive | RSA TCE simplified |
|---|---|---|---|---|---|
| Refractory status (number of treatment classes) | - | Yes | 1 | Included (Forced)[a] | Yes |
| Cytogenetic risk profile | Yes | Yes | 3 | Included (Forced)[a] | Overall R-ISS included |
| ISS/R-ISS disease stage | - | - | 3 | Individual components | Yes (R-ISS) |
| Age | - | Yes | 3 | Included (Forced)[a] | Yes |
| Extramedullary disease | - | Yes | 5.5 | Not available | |
| Time to progression on last regimen | - | - | 6.5 | Excluded by Cox regression | |
| Exposure status (number of prior lines) | - | - | 7 | Included (100%)[b] | |
| Lactate dehydrogenase (LDH) | Yes | Yes | 7.5 | Included (Forced)[a] | Overall R-ISS included |
| Time since diagnosis (TSD) | - | - | 9 | Included (100%)[b] | Yes |
| Hemoglobin | - | - | 10.5 | Included (100%)[b] | |
| ECOG performance status | - | Yes | 11 | Included (100%)[b] | |
| Bone marrow plasma cell count | - | Yes | 13.5 | Not available | |
| Platelet count | - | - | 14.5 | Included (100%)[b] | |
| B2 microglobulin | Yes | Yes | 15.5 | Included (Forced)[a] | Overall R-ISS included |
| Prior stem cell transplantation (SCT) | - | - | 16.5 | Included (100%)[b] | |
| Biochemical vs clinical relapse | - | - | 18 | Not available | |
| Bone lesions | - | Yes | 18.5 | Not available | |
| Best response to last prior therapy | - | - | 18.5 | Not available (≥ 40% missing) | |
| Time to next treatment in the last line | - | Yes | 19 | Not available at baseline | |
| Prior therapy with IMiD agent | - | - | 19.5 | Not relevant | |
| MM type/immunoglobulin type | - | - | 20 | Not available (≥ 40% missing) | |
| Calcium | - | Yes | 20 | Excluded by Cox regression | |
| Albumin | Yes | Yes | 20.5 | Included (Forced)[a] | Overall R-ISS included |

Purple shading indicates the characteristics included in the RSA. Lighter shading signifies variables selected for inclusion based on Cox regression; darker shading signifies forced variables due to high ranking and clinical relevance. The RSA DCE comprehensive had similar results as the RSA TCE comprehensive. Severe toxicity, sex, bridging therapy, and race excluded prior to Cox model due to low rank. Prior therapy with IMiD agent excluded from the DCE RSA by Cox regression. Calcium was included in the DCE RSA. The characteristics included in the RSA TCE simplified also apply to the RSA DCE simplified. [a]Predictor was included in the model independent of statistical significance; [b]Percentages indicate the number of times a covariate was selected across imputed datasets. ECOG, Eastern Cooperative Oncology Group.

**Table 2. Patient characteristics estimates of predictors in the DCE and TCE RSAs**

| Characteristics | DCE cohort (N = 7824) | | | TCE cohort (N = 2823) | | |
|---|---|---|---|---|---|---|
| | Completeness | Summary | Adjusted HR (95% CI) | Completeness | Summary | Adjusted HR (95% CI) |
| **Age, years, n (%)** | 100% | | | 100% | | |
| ≤ 65 (0)[a,b] | | 4891 (63) | | | 1110 (39) | |
| > 65 (Age − 65)[b] | | 2993 (38) | 1.031 (1.024, 1.038) | | 1713 (61) | 1.022 (1.011, 1.033) |
| **ECOG performance status, n (%)** | 65% | | | 71% | | |
| 0 | | 1538 (30) | 1 (ref) | | 579 (29) | 1 (ref) |
| 1 | | 2337 (46) | 1.317 (1.197, 1.449) | | 941 (47) | 1.060 (0.897, 1.253) |
| 2 | | 915 (18) | 1.598 (1.422, 1.795) | | 361 (18) | 1.397 (1.144, 1.706) |
| ≥ 3 | | 320 (6) | 2.404 (2.023, 2.857) | | 135 (7) | 1.778 (1.350, 2.342) |
| **TSD, months, n (%)** | 100% | | | 100% | | |
| $< 4 \left(\frac{TSD-4}{12}\right)^b$ | | 651 (8) | 0.808 (0.282, 2.311) | | 52 (2) | 0.507 (0.356, 0.721) |
| $\geq 4 \left(\frac{TSD-4}{12}\right)^b$ | | 7173 (92) | 1.024 (1.002, 1.046) | | 2771 (98) | 1.001 (0.998, 1.003) |
| **Cytogenetic risk, n (%)** | 39% | | | 44% | | |
| Standard | | 2036 (68) | 1 (ref) | | 768 (62) | 1 (ref) |
| High | | 977 (32) | 1.528 (1.366, 1.709) | | 471 (38) | 1.369 (1.138, 1.648) |
| **LDH, n (%)[c]** | 29% | | | 35% | | |
| < the upper limit of normal | | 1708 (75) | 1 (ref) | | 705 (71) | 1 (ref) |
| ≥ the upper limit of normal | | 583 (25) | 1.529 (1.339, 1.746) | | 285 (29) | 1.673 (1.379, 2.030) |
| **B2 microglobulin, mg/L, n (%)** | 21% | | | 20% | | |
| < 5.5 (B2 − 5.5)[b] | | 1262 (77) | 1.169 (1.114, 1.227) | | 436 (78) | 1.232 (1.133, 1.340) |
| ≥ 5.5 (0)[b,d] | | 380 (23) | | | 120 (22) | |
| **Albumin, g/dL, mean (SD)** | 78% | 3.7 (1) | 0.722 (0.668, 0.780) | 81% | 3.7 (1) | 0.632 (0.556, 0.719) |
| **Hemoglobin, g/dL, mean (SD)** | 84% | 11.3 (2) | 0.937 (0.914, 0.960) | 84% | 11.1 (2) | 0.921 (0.088, 1.003) |
| **Platelet count, $10^9$/L, mean (SD)[b,e]** | 76% | 190.3 (89) | 0.864 (0.822, 0.908) | 74% | 180.2 (88) | 0.803 (0.734, 0.879) |
| **Calcium, mmol/L, n (%)[f]** | 78% | | | 80% | | |
| 8.5-10.5 | | 5034 (83) | 1 (ref) | | 1837 (82) | - |
| < 8.5 or > 10.5 | | 1032 (17) | 1.145 (1.034, 1.269) | | 418 (19) | - |
| **Refractory status (number of treatment class), n (%)** | 49% | | | 42% | | |
| 0 | | 2221 (58) | 1 (ref) | | 455 (38) | 1 (ref) |
| 1-2 | | 1628 (42) | 1.135 (1.033, 1.247) | | 367 (31) | 1.153 (0.930, 1.429) |
| 3 | | 0 | - | | 372 (31) | 1.184 (0.947, 1.479) |
| **Number of prior lines, n (%)** | 100% | | | 100% | | |
| 1 | | 5605 (72) | 1 (ref) | | 472 (17) | 1 (ref) |
| 2 | | 1858 (24) | 1.147 (1.055, 1.246) | | 1019 (36) | 1.590 (1.190, 2.126) |
| 3 | | 361 (5) | 1.166 (1.001, 1.358) | | 647 (23) | 1.983 (1.451, 2.710) |
| ≥ 4 | | 0 | - | | 685 (24) | 1.884 (1.369, 2.592) |
| **Prior SCT, n (%)** | 100% | | | 100% | | |
| No | | 4682 (60) | 1 (ref) | | 14.0 (50) | 1 (ref) |
| Yes | | 3142 (40) | 0.561 (0.511, 0.616) | | 1422 (50) | 0.698 (0.595, 0.819) |

Age (< 65 years), TSD, and B2 microglobulin (< 5.5 mg/L) were modeled as continuous variables in the Cox regression models. ISS and R-ISS were manually derived from B2 microglobulin, albumin, LDH and cytogenetic risk; ISS and R-ISS were missing for 80.1% and 94.9% of patients in the DCE cohort, respectively; ISS and R-ISS were missing for 81.2% and 93.6% of patients in the TCE cohort, respectively. [a]Values of ≤ 65 years were set to 0 before fitting the Cox regression, resulting in a constant risk for all patients aged ≤ 65 years; [b]Variable transformation to capture non-linearity of the predictor-OS association; [c]Categories were defined in the Flatiron dataset; [d]Values of ≥ 5.5 mg/L were set to 0 before fitting the Cox regression, resulting in a constant risk for all patients with B2 microglobulin ≥ 5.5 mg/L; [e]Transformation for platelet count was linear decreasing risk until 450 × $10^9$/L then constant risk beyond; [f]Calcium was included only for DCE RSA. CI, confidence interval; HR, hazard ratio; ref, reference; SD, standard deviation.

## Results

### Study population

- A total of 7824 and 2823 patients were included in the DCE and TCE cohorts, respectively
  - The characteristics of patients at baseline are summarized in **Table 2**
  - The median (range) follow-up based on OS event times was 20.1 months (0.1-152.6) for the DCE cohort and 11.1 months (0.1-94.9) for the TCE cohort
- Independent predictors of OS in both RSAs (DCE and TCE) included age, ECOG performance status, TSD, cytogenetic risk, LDH, B2 microglobulin, albumin, hemoglobin, platelet count, calcium level (only for DCE), refractory status (number of treatment classes), number of prior lines, and prior SCT (**Table 1** and **Table 2**)
- The simplified RSA model is shown in **Table 3**

**Table 3. Simplified RSA modeling of prognostic effects in the DCE and TCE cohorts**

| Prognostic factor | Condition | Predictor value | Adjusted HR (95% CI) DCE | Adjusted HR (95% CI) TCE |
|---|---|---|---|---|
| **R-ISS** | I | | 1 (ref) | |
| | II | | 2.126 (1.870, 2.416) | 2.520 (1.967, 3.228) |
| | III | | 4.399 (3.623, 5.343) | 6.147 (4.492, 8.411) |
| **Refractory status** | 0 | | 1 (ref) | |
| | 1 or 2 | | 1.371 (1.261, 1.491) | 1.560 (1.267, 1.920) |
| | 3 | | - | 1.907 (1.545, 2.353) |
| **Age,[a,b] years** | Age ≤ 65 | 0 | 1.064 (1.058, 1.070) | 1.039 (1.030, 1.049) |
| | Age > 65 | *Age − 65* | | |
| **TSD[b]** | TSD < 4 months | *TSD − 4* | - | 0.527 (0.383, 0.725) |
| | TSD ≥ 4 months | *TSD − 4* | - | 1.0004 (0.998, 1.003) |
| | TSD < 0.3 years | *TSD − 0.3* | 0.132 (0.048, 0.364) | - |
| | TSD ≥ 0.3 years | *TSD − 0.3* | 1.002 (0.982, 1.022) | - |

Age (≤ 65 years) and TSD were modeled as continuous variables in the Cox regression models. [a]Values of ≤ 65 years were set to 0 before fitting the Cox regression, resulting in a constant risk for all patients aged ≤ 65 years; [b]Variable transformation to capture non-linearity of the predictor-OS association. This model has the same risk for patients aged ≤ 65 years vs those aged > 65 years.

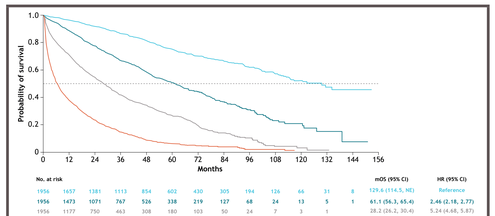
### Stratification of patients

- For the DCE cohort, significant differences in OS between the 4 (Low, Medium, High, and Very-high) risk groups were observed (**Figure 1**)
  - Median OS was 130, 61, 28, and 7 months, respectively, in groups 1 (lowest risk) to 4 (highest risk)
- Significant differences in OS between the 4 (Low, Medium, High, and Very-high) risk groups were also observed for the TCE cohort (**Figure 2**)
  - Median OS was not reached, 46, 17, and 4 months, respectively, in groups 1 to 4
- Similar stratification was observed across risk groups defined by the simplified RSAs (**Figure 3**)

### Validation of RSA using PFS

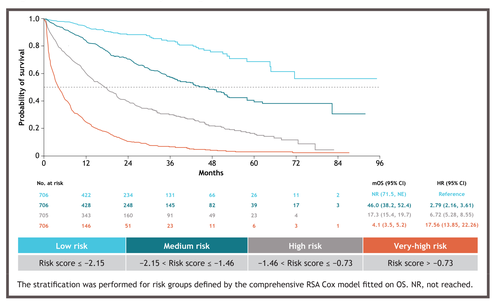
- When the RSA was applied to PFS, differences in PFS between risk groups were significant for both the DCE and TCE cohorts
  - TCE cohort: median PFS was 9, 6, 4, and 2 months for the Low, Medium, High, and Very-high risk groups, respectively (**Figure 4**)
  - Similar results were observed for the DCE cohort (data not shown)

**Figure 1. OS stratified by risk group in DCE RRMM**



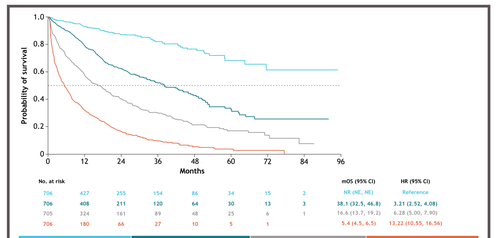

The stratification was performed for risk groups defined by the comprehensive RSA Cox model fitted on OS. mOS, median OS; NE, not estimable.

**Figure 2. OS stratified by risk group in TCE RRMM**



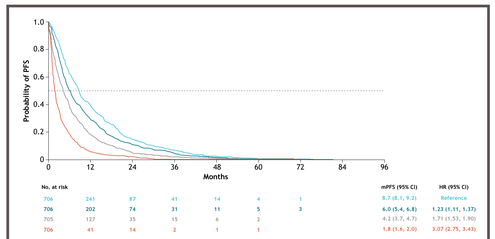

The stratification was performed for risk groups defined by the comprehensive RSA Cox model fitted on OS. NR, not reached.

**Figure 3. Risk groups defined by simplified RSA in the TCE cohort**




The stratification was performed for risk groups defined by the simplified RSA Cox model fitted on OS.

**Figure 4. PFS stratified by risk groups in TCE RRMM**




The stratification was performed for risk groups defined by the comprehensive RSA Cox model fitted on PFS. mPFS, median PFS.

## Limitations

- DCE and TCE RSAs developed in this study may not be generalizable to other patient populations such as patients outside of the USA or patients who are penta-exposed or triple-class refractory
- Real-world data analysis may be affected by quality issues (eg, missing data on important prognostic factors) and variability in patient and disease characteristics and outcomes, which may reduce the predictive accuracy of the model if this variability is not accounted for
- The treatment landscape of RRMM has dramatically changed during the 13-year study period, which may make some of the data collected less applicable to the current treatment landscape

## Conclusions

- RSAs for patients with DCE and TCE RRMM were developed using the Flatiron Health database with high statistical power that can quantify total risk and patient-specific risk, which can be used to inform clinical decision-making and tailor management strategies for patients
- Future studies are warranted to validate the RSA in an external dataset

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