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Development and Validation of a Simplified Score to Predict Early Relapse in Newly Diagnosed Multiple Myeloma in a Pooled Dataset of 2,190 Patients

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(Article begins on next page)

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Research article

Developing and Validating a Simplified Score to Predict Early Relapse in Newly Diagnosed Multiple Myeloma (S-ERMM): Analysis from a Pooled Dataset of 2190 Patients

Running title: S-ERMM: A Simplified Early Relapse in Multiple Myeloma Score

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Competing interests
MTP has received honoraria from and has served on the advisory boards for Celgene, Janssen-Cilag, Amgen, Bristol-Myers Squibb, Takeda, Sanofi, and GSK.
MO has received honoraria from and has served on the advisory boards for Amgen, Bristol-Myers Squibb, Celgene, GSK, Janssen, Sanofi, and Takeda.
PC has participated as lecturer and/or has served on the advisory boards for AbbVie, ADC Therapeutics, Amgen, Celgene, Daiichi Sankyo, Gilead, Incyte, Janssen, Jazz Pharmaceuticals, Kite, Kyowa Kirin, Novartis, Roche, Sanofi, Servier, and Takeda.
AML has received personal fees from Incyte; has received research funding from Novartis, Janssen, AbbVie, Roche, Celgene, Amgen, Bristol-Myers Squibb, Takeda, Incyte, Pfizer, Beigene, Oncopeptides, Verastem, Karyopharm, Archigen, Biopharma, Debiopharm, Morphosys, Fibrogen, and Onconova.
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AB has served on the advisory boards for Janssen, Celgene, and Amgen.
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MB has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol-Myers Squibb, and AbbVie; has served on the advisory boards for Janssen and GSK; has received research funding from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol-Myers Squibb, and Mundipharma.
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The remaining authors declare no competing financial interests.

Data Sharing

After the publication of this article, data collected for this analysis and related documents will be made available to others upon reasonably justified request, which has to be written and addressed to the attention of the corresponding author Dr. Francesca Gay at the following e-mail address: fgay[*at*]cittadellasalute.to.it. The corresponding author Dr. Francesca Gay is responsible to evaluate and eventually accept or refuse every request to disclose data and their related documents, in compliance with the ethical approval conditions, in compliance with applicable laws and regulations, and in conformance with the agreements in place with the involved subjects, the participating institutions, and all the other parties directly or indirectly involved in the participation, conduct, development, management and evaluation of this analysis.

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Statement of translational relevance

Despite the huge amount of literature, there is a lack of consensus on how to better predict early relapse (ER) in patients with multiple myeloma (MM). We pooled data from 7 European clinical trials enrolling 2190 patients with newly diagnosed MM from October 2003 to March 2017 to develop the Simplified Early Relapse in Multiple Myeloma (S-ERMM) score. This analysis provided further evidence of the critical role of predicting ER in MM patients, which is strongly associated with poor outcome. The S-ERMM predicted ER by using simple and widely available baseline features. After external validation, the future development of this prognostic index may consider its combination with other static-risk features (genomic abnormalities, circulating tumor cells) and dynamic risk evaluation (response to the therapy such as minimal residual disease) for ER prediction. The identification of high-risk patients with dismal prognosis is the first step towards a better design of therapeutic approaches for this patient subgroup.

Abstract

Background. Despite the improvement of therapeutic regimens, several multiple myeloma (MM) patients still experience early relapse (ER). This subset of patients currently represents an unmet medical need.

Methods. We pooled data from 7 European multicenter phase II/III clinical trials enrolling 2190 newly diagnosed (ND)MM patients from 2003 to 2017. Baseline patient evaluation included 14 clinically relevant features. Patients with complete data (n=1218) were split into training (n=844) and validation sets (n=374). In the training set, a univariate (UV) analysis and a multivariate (MV) logistic regression model on ER within 18 months (ER18) were made. The most accurate model was selected on the validation set. We also developed a dynamic version of the score by including response to treatment.

Results. The Simplified Early Relapse in MM (S-ERMM) score was modeled on 6 features weighted by a score: 5 points for high lactate dehydrogenase or t(4;14); 3 for del17p, abnormal albumin or bone marrow plasma cells >60%; and 2 for λ free-light chain. The S-ERMM identified 3 patient groups with different risks of ER18: Intermediate (Int) vs. Low (OR=2.39, p<0.001) and High vs. Low (OR=5.59, p<0.001). S-ERMM High/Int patients had significantly shorter OS (High vs. Low: HR=3.24, p<0.001; Int vs. Low: HR=1.86, p<0.001) and PFS2 (High vs. Low: HR=2.89, p<0.001; Int vs. Low: HR=1.76, p<0.001) than S-ERMM Low. The Dynamic (D)S-ERMM modulated the prognostic power of the S-ERMM.

Conclusion. Based on simple, widely available baseline features, the S-ERMM and DS-ERMM properly identified patients with different risks of ER and survival outcomes.

1. Introduction

In the past few years, the prognosis of patients with multiple myeloma (MM) has been markedly improved by the introduction of new drugs and better therapeutic strategies both at diagnosis and at relapse (1–4). Traditionally, the maximal benefit in terms of duration of remission has been observed with first-line therapies. With the use of high-dose chemotherapy and autologous stem-cell transplantation (ASCT) combined with novel agents or the adoption of multi-targeted agents including immunomodulatory (IMiD) agents, proteasome inhibitors (PIs) and monoclonal antibodies, the current median progression-free survival (PFS) of newly-diagnosed (ND)MM patients ranged between 41 and 50 months (4,5). Despite this remarkable improvement, still a significant proportion of patients experiences an early relapse (ER), which has been associated with a dismal prognosis. Several studies reported the association of baseline clinical features with ER (6–12), but there is no clear consensus on what are the most important determinants; as a matter of fact, even patients without well-known high-risk features at baseline may relapse early (7,13). Data published so far mainly come from registries or from retrospective analyses that do not systematically consider updated standard-of-care risk assessments (e.g. cytogenetics, Revised-International Staging System [R-ISS]) (12).

Unfortunately, a consensus on the appropriate definition of ER is also lacking. So far, it has been defined as relapse within either 12/18 months from the start of induction treatment (10,12) or 12/24 months from transplantation (6–9,11,14,15).

Indeed, patients with ER have an inferior prognosis, as compared to patients who relapse later and, as such, represent a high-risk group and an unmet medical need (12,14).

The correct identification of patient risk at baseline is the first step toward a risk-adaptive therapeutic approach. The aim of our analysis was to develop and validate the Simplified Early Relapse in Multiple Myeloma (S-ERMM), a score to predict the risk of ER based on widely available clinical and biological features. Thereafter, the S-ERMM score was re-modulated during the patient clinical course by integrating response to therapy. We also aimed to correlate the S-ERMM with the long-term outcomes overall survival (OS) and PFS2.

2 Methods

2.1 Source of data and participants

Individual patient data from 2190 NDMM patients enrolled in seven multicenter European, open-label, phase II/III clinical trials evaluating novel agent-based therapies from October 2003 to March 2017 were pooled together and analyzed: NCT01093196, NCT01346787, NCT01857115, NCT01190787, NCT00551928, NCT01091831, NCT02203643 (2,3,16–20). Each study was approved by ethics committees or institutional review boards at the respective study sites and was conducted in accordance with the Declaration of Helsinki; all patients provided written informed consent. All patients received new drugs (IMiD agents and/or PIs) as upfront treatment, with or without transplantation. Trial details, treatment schedules and eligibility criteria are reported in Supplementary Tables S1A-B.

2.2 Prognostic factors and outcomes

Data were retrieved from electronic case-report forms (eCRFs). All the available individual baseline features were analyzed. Age, creatinine levels, albumin, β2-microglobulin (β2m) and monoclonal plasma cells in the bone marrow (BMPCs) were evaluated as continuous features. According to the International Myeloma Working Group recommendations, the

percentage of BMPCs considered was the highest in case of discrepancy between BM biopsy and BM aspirate (21).

Free light chain (FLC, λ vs. κ), M-component subtype (IgA vs. others), lactate dehydrogenase (LDH) levels >/≤upper limit of normal (ULN), presence vs. absence of plasmacytomas, presence vs. absence of chromosomal abnormalities (CAs) detected by interphase fluorescence *in situ* hybridization [iFISH; del17p, t(4;14), t(14;16), t(11;14)] were evaluated as categorical values. iFISH analysis was centralized in one laboratory (see the Supplementary Methods). High-risk CAs were defined as the presence of del(17p) and/or t(4;14) and/or t(14;16). (22) The cut-offs for del(17p) and IgH translocation were 10% and 15%, respectively. Baseline R-ISS stage (II/III vs. I) was also included in the prognostic factor evaluation (23). Patients with complete data were then split into training and validation sets. In the validation set, patients treated with more innovative and effective therapies were included. These patients also had a shorter median follow-up.

Based on the available literature, two cut-offs for ER were evaluated: 18 (ER18) and 24 (ER24) months from diagnosis. In the ER18 analysis, patients who died for reasons other than progressive disease (PD) or who withdrew consent within 18 months were excluded from the analysis because they were not at risk of progression for the entire first 18 months. Patients experiencing PD within 18 months from diagnosis were included in the ER18 population; those not experiencing PD within 18 months were included in the reference population. The reference population was then divided into 2 groups: patients experiencing PD after 18 months from diagnosis at the time of their last follow-up (Late relapse group) and patients who were free from progression at the time of their last follow-up (No PD group).

Methods for the ER24 analysis were similar, but they included a cut-off of 24 months after diagnosis (see the Supplementary Appendix). The results regarding the best cut-off are reported in the main text of this contribution. For the sake of completeness, the other analyses are included in the Supplementary Appendix.

OS was calculated from the start of treatment until the date of death or the date the patient was last known to be alive. PFS2 was calculated from the start of treatment until the date of PD after the second line of treatment (second PD) or death (regardless of the cause of death), whichever came first. Other clinical endpoints are detailed in the Supplementary Methods.

2.3 Statistical analysis

From the training set, a univariate analysis (UV) on ER18 as outcome was performed according to chi-square and Kruskal-Wallis tests, as appropriate. Features with $p<0.1$ were then tested in a multivariate (MV) logistic regression model. We compared 2 MV analyses, one including the R-ISS and the other including individual features defining the R-ISS (LDH, albumin, β2m and CAs). In order to account for potential confounders, each MV analysis was adjusted for age. Subsequently, each MV analysis was identified through a backward selection based on the minimization of the Akaike Information Criterion to identify independent prognostic factors. Continuous parameters were not categorized a priori because this would have negatively affected the power of the analysis. After selecting the best MV model, the optimal cut-offs for the most significant continuous features were re-evaluated by spline function. MV models were used to estimate odds ratio (OR) for ER18 risk, 95% confidence intervals (CIs) and p-values.

Each model was tested on the validation set by assessing the area under the curve (AUC), in order to select the most accurate model including individual features or features aggregated into the R-ISS.

Once the most accurate model was selected, three prognostic groups of patients with Low, Intermediate (Int) and High risk of ER were defined by categorizing the linear predictors of the final MV logistic model. Hence, two optimal cut-points were found maximizing the ORs defined by the MV in the training set. A scalar score was thus proportionally assigned to each predictor according to the coefficients of the final MV model. As the linear score, two optimal cut-points were found maximizing the ORs defined by the MV in both the training and validation sets. Thus, we developed the S-ERMM score, which identified three different groups of patients with Low, Int, and High risks of ER18. Other statistical survival analyses are detailed in the Supplementary Methods.

In order to integrate baseline prognostic evaluation and response to treatment, we developed the Dynamic (D)S-ERMM, a logistic model that included S-ERMM score and achievement of at least a very good partial response (≥VGPR). Since this score included response, it should not be assessed at baseline, but at a subsequent timepoint after treatment, in order to re-modulate patient risk during therapy (dynamic risk score). We therefore analyzed data from a landmark point, which was set at the median time to achieve ≥VGPR and included only patients who did not relapse before the landmark point. We assessed the role of ≥VGPR and S-ERMM in a MV logistic regression model to predict ER18. The DS-ERMM was modeled on the proportional coefficients obtained from the MV model. To measure the prognostic performances on this sub-cohort, we compared the concordance (C)-index assessed in both models (24).

Statistical analysis was performed using R (v.3.5.2). We used the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD) criteria to validate our methods (25,26).

3 Results

3.1 Patient characteristics

Data from 2190 patients were available; 3 patients were excluded because of screening failure.

In the ER18 analysis, 50 patients died for reasons other than PD and 51 withdrew their consent within 18 months and were excluded; patients eligible for the analyses were 2086. Patients with complete data (n=1218) were then split into training (n=844) and validation (n=374) sets and included in the logistic regression analysis.

Training set: in the overall population (median follow-up 70 months, interquartile range [IQR]=48-81 months), the median age was 66 years, 73% of patients presented with R-ISS stage II/III, 10% with LDH>ULN; 14% with del(17p), 14% with t(4;14). Patients with BMPCs>60% were 29% and 36% had λ FLC. A total of 312/844 (37%) patients experienced ER18. Patients in the ER18 vs. the reference population were significantly older (p=0.026), had higher β2m (p<0.001) and lower albumin (p<0.001) levels; a higher proportion of patients had LDH>ULN (p=0.001), t(4;14) (p<0.001), R-ISS stage II/III (p<0.001), del17p (p=0.005) and BMPCs>60% (p=0.001; Table 1).

Validation set: in the overall population (median follow-up 35 months, IQR 29-41), the median age was 57 years, which was significantly lower (p<0.001) than that in the training set. Patients who experienced ER18 were 61/374 (16%). The distribution of baseline features between ER18 and the reference population was similar to that in the training set, except for the absence of significant difference in the proportion of patients with BMPCs>60% and del(17p), although this may be related to the smaller sample size (Table 1).

The median time to ≥VGPR was 9 months in the training set and 3 months in the validation set. ≥VGPR at 9 months was achieved in 40% and 81% of patients in the training and validation sets, respectively.

3.2 Best model of ER

Based on the UV analysis of patients who experienced ER18, 10/14 features were included in the MV analysis: age, FLC, BMPCs, del17p, t(4;14), t(14;16), albumin, β2m, LDH, and R-ISS stage. In the MV analysis incorporating the R-ISS, age, R-ISS II/III vs. I and increased BMPCs increased the risk of ER18. When the MV analysis was performed including single features defining the R-ISS, increased BMPCs, λ FLC, LDH>ULN, presence of del17p, and t(4;14) increased the probability of ER18 (Table 2).

Each MV model was then tested on the validation set. The AUC was 0.62 (95% CI=0.55-0.69) for the ER18 model including the R-ISS and 0.66 (95% CI=0.58-0.73) for the ER18 model incorporating individual features. The ER18 model incorporating individual features resulted in the highest AUC (0.66) and was therefore selected to develop the S-ERMM score.

UV and MV ER24 analyses and the AUC in the validation set are reported in the Supplementary Results and in Table S3.

3.3 S-ERMM score

The ER18 linear index was calculated as 0.047 × BMPCs %/5 + 0.589 × LDH/ULN (IF LDH>ULN) + 0.459 × del17p (IF present) + 0.705 × t(4;14) (IF present) + 0.293 × FLC (IF λ) - 0.284 × albumin.

In the training set, the linear score significantly discriminated three patient groups (High, intermediate [Int] and Low risk) with significantly different risks of ER18 (Figure 1).

BMPC and albumin levels were dichotomized according to the optimal cut-off: high BMPC level if >60% and abnormal albumin level if ≤3.5 or ≥5 (Figure S1).

The S-ERMM score (https://sermm.emnitaly.org/) was mathematically consistent with the linear index and was defined including 6 features identified in the MV analysis: 5 points for LDH>ULN or the presence of t(4;14); 3 points for the presence of del17p, abnormal albumin and BMPCs>60%; and 2 points for the presence of λ FLC (Figure 1).

The Low-risk group included patients with a total score ≤5 (68% of patients in the training set, 29% of whom experienced an ER18); the Int-risk group patients with a total score between 6 and 10 (25% of patients in the training set, 50% of whom with ER18); and the High-risk group patients with a total score ≥11 (7% of patients in the training set, 70% of whom with ER18). In the training set, the S-ERMM significantly discriminated three groups of patients with different risks of ER18: Int vs. Low (OR=2.39, 95% CI=1.73-3.30, p<0.001) and High vs. Low (OR=5.59, 95% CI=3.08-10.16, p<0.001). The S-ERMM was confirmed in the validation set: Int vs. Low (OR=2.27, 95% CI=1.23-4.17, p=0.008) and High vs. Low (OR=4.87, 95% CI=2.01-11.76, p=0.001). The impact of the S-ERMM on the ER18 risk was higher than that of each single feature.

In the DS-ERMM analyses, the training population (n=673) included patients evaluable for response at 9 months (median time to ≥VGPR), 162 (24%) of whom experienced ER18. In this population, both the S-ERMM and the achievement of ≥VGPR were statistically independent predictors of ER in the MV analysis (Figure S2).

The DS-ERMM score was defined as the S-ERMM score obtained at baseline minus 4 points in case of achievement of ≥VGPR. Patients who reached the 9-month cut-off (which was not

reached by 171 patients, 150 of whom relapsed/died before), were thus reclassified in three groups: the Low-risk group included 250 patients (37%) with a total score ≤0 (only 12% of whom experienced an ER18); the Int-risk group included 271 patients (40%) with a total score between 1 and 5 (only 24% of whom with ER18); and the High-risk group included 152 patients (23%) with a total score ≥6 (45% of whom with ER18). These three groups had different risks of ER18 (Figure S3): Int vs. Low (OR=2.36, 95% CI=1.46-3.80, p<0.001) and High vs. Low (OR=6.34, 95% CI=3.84-10.46, p<0.001).
In the validation set, there were no significant differences in terms of risk of ER18 between DS-ERMM Int vs. Low, while a trend towards a higher risk was observed in the High vs. Low comparison (OR=2.40; p=0.09; see the Supplementary Results).
Following the application of the S-ERMM score at baseline and the re-modulation of patient risk at 9 months according to DS-ERMM (for those patients who did not relapse during the first 9 months), 20% of patients in the total population of the training set were classified as High-risk patients, 39% as Int-risk patients, and 41% as Low-risk patients.

3.4 Survival analysis

A landmark analysis with landmark point at 18 months was performed. OS and PFS2 were significantly shorter in the ER18 population than in the reference population and the Late relapse and No relapse populations (Figures S4A-D). Similarly, ER18 patients showed an inferior outcome after relapse (Supplementary Results and Figure S5).
The median OS was 31.5 months in patients with S-ERMM High, 59.5 with S-ERMM Int and not reached (NR) with S-ERMM Low. Median PFS2 was 19.8 months in patients with S-ERMM High, 40.0 months with S-ERMM Int and 62.3 months with S-ERMM Low. OS and PFS2 were significantly shorter in S-ERMM Int vs. S-ERMM Low patients (OS, HR=1.86, 95% CI=1.48-2.33; PFS2, HR=1.76, 95% CI=1.45-2.14; both p<0.001) and in S-ERMM High vs. S-ERMM lnt patients (OS, HR=1.74, 95% CI=1.22-2.50, p=0.002; PFS2, HR=1.64, 95% CI=1.18-2.28; p=0.003; Figure 2). The median PFS was 31.6 months in S-ERMM Low, 17.3 months in S-ERMM Int, and 13.2 months in S-ERMM High patients.
Subgroup analyses for OS according to first-line treatment confirmed the prognostic role of S-ERMM in ASCT-ineligible patients (Int vs. Low, HR=1.75, 95% CI=1.30-2.35, p<0.001; High vs. Int, HR=1.85, 95% CI=1.10-3.11, p=0.020) and in ASCT-eligible patients (Int vs. Low, HR=1.94, 95% CI=1.36-2.78, p<0.001; High vs. Int, HR=1.81, 95% CI=1.09-3.01, p=0.022) (Figure S6); in PI-treated patients (Int vs. Low, HR=1.73, 95% CI=0.93-3.20, p=0.083; High vs. Int, HR=3.13, 95% CI=1.21-8.08, p=0.018); and in patients treated with IMiD agents (Int vs. Low, HR=1.85, 95% CI=1.45-2.37; p<0.001; High vs. Int, HR=1.64, 95% CI=1.11-2.43, p=0.013).
According to DS-ERMM, OS and PFS2 were significantly shorter in DS-ERMM Int vs. DS-ERMM Low patients (OS, HR=1.96, 95% CI=1.44-2.66; PFS2, HR=1.86, 95% CI=1.44-2.38; both p<0.001) and in DS-ERMM High vs. DS-ERMM Low patients (OS, HR=3.28, 95% CI=2.37-4.54, p<0.001; PFS2, HR=2.91, 95% CI=2.22-3.82; p<0.001; Figure 3).

4 Discussion

Several studies reported dismal survival outcomes in MM patients experiencing an ER; however, the definition of ER varies from study to study, and consensus is still lacking. Also, the impact of well-known disease-related risk factors (e.g., albumin, β2m, CAs by iFISH and LDH) on the risk of ER has not been thoroughly assessed in NDMM patients. The correct evaluation of baseline ER risk thus remains an unmet medical need.

We confirmed ER with an 18-month cut-off as a strong predictor of the long-term outcomes' OS and PFS2 in the context of novel-treatment approaches (e.g., PIs, IMiD agents and ASCT). Our decision of adopting the 18-month cut-off for the definition of ER was also supported by the available literature, in which most of the studies defined ER as both 18 months from diagnosis and 12 months from ASCT (6–10,12,27).

We developed the S-ERMM score by identifying and integrating 6 features that predicted the risk of ER (presence of t(4;14), del17p, LDH>ULN, BMPCs>60%, abnormal albumin and λ FLC). S-ERMM is a simple tool enabling the identification of 3 patient groups with significantly different risks of ER (Figure 2) and significantly different PFS2 and OS. In particular, S-ERMM High patients had a median OS of 31 months, significantly shorter than that of S-ERMM Int (median 60 months) and S-ERMM Low patients (median NR after 6 years of follow-up).

Although several studies tried to correlate ER risk with clinical and biological features (6–9,11,12,14), most of them did not cover all of the recognized MM prognostic factors (23) [e.g. extensive CA analysis (8,9,14) and LDH assessment (10)]. In our series, we included widely available and well-recognized baseline features. The S-ERMM score included albumin levels (which reflect the inflammatory state at diagnosis) (28), high-risk CAs (del17p and t(4;14), associated with a biologically aggressive disease), and high LDH (29) and BMPC levels (associated with tumor burden) (30).

The majority of analyses published so far on ER in MM are single-center or retrospective studies. To the best of our knowledge, only Bygrave et al. analyzed young ASCT-eligible patients enrolled in a single clinical trial (7). Indeed, in our analysis, data from clinical trials underwent a systematic data assessment, with baseline features assessment, centralized laboratory analyses and uniform evaluation of response and clinical outcomes (31). In this light, the development and validation of the S-ERMM score in a population consisting of both young (transplant-eligible) and elderly (>65 years) patients enrolled in 4 phase II/III clinical trials treated with novel agents from different drug classes with or without ASCT support the application of this score to NDMM patients. On the other hand, this is a selected population of European clinical trials that indeed needs validation in real-life settings.

Response to therapy is a strong predictor of better OS and PFS2 (15), and the achievement of a deep response (minimal residual disease [MRD] negativity) may abrogate the poor prognosis conferred by high-risk FISH at diagnosis. Therefore, the importance of integrating static (baseline) and dynamic (response) prognostic features led to the incorporation of response to treatment (≥VGPR) into the S-ERMM score. The assessment of the S-ERMM score at the time of diagnosis and the re-modulation of patient risk at 9 months (for those patients who did not relapse during the first 9 months) improved our ability to detect ER patients. In fact, in the initial population of our analysis, only 7% of patients were included in the high-risk group (S-ERMM High), while 68% of patients were included in the S-ERMM Low group (29% of whom had an ER18) and 25% in the S-ERMM Int group (50% of whom had an ER18). Of note, in the DS-ERMM analysis, the Low-risk group included only 37% of patients (with only 12% who had an ER18) and the Int-risk group 40% of patients (with only 24% who had an ER18). Ultimately, using sequentially these two scores in the overall population, 20% of patients were determined to be at High risk, 39% at Int risk, and 41% at Low risk. This improvement in the evaluation of patient risk of ER highlighted the role of the dynamic modulation of patient risk at baseline.

Unfortunately, in the validation set, there were no significant differences in terms of risk of ER18 between DS-ERMM Int vs. Low, while trends towards a higher risk were observed in the High vs. Low comparison.

Of note, the optimal response (degree and timing) to be incorporated as a dynamic factor should consider the type of patient population and the availability of treatment options:

472 these two factors determine the choice of a specific therapy, with different degrees of
473 efficacy and time to best response. In the validation set, the rate of ≥VGPR was definitely
474 higher than in the training set and the median time to response was lower. We presume
475 that the assessment of a deeper response, such as the achievement of MRD negativity, could
476 better discriminate patients in the context of novel, highly effective therapies.
477 Unfortunately, MRD evaluation was not available in most of the trials included in the
478 training set and could not be used as optimal response to recalculate the risk of ER after
479 therapy. Still, our main aim was to identify patients at risk of ER using risk assessment at
480 diagnosis, and the S-ERMM score was prognostic in the context of both older (training set)
481 and more recent (validation set) drug regimens.
482 Our analysis has some limitations. First, the risk classification based on the S-ERMM score
483 was designed to better identify patients at high risk of ER and, as a consequence, was
484 unbalanced, with only a small proportion of patients in the S-ERMM High group.
485 Nevertheless, the risk group stratification improved after the re-modulation of risk
486 assessment by using the DS-ERMM score.
487 Another limitation was the low number of patients treated upfront with a combination of
488 PIs and IMiD agents in the training set, since this currently represents a standard of care
489 for both young and elderly patients. Nevertheless, our results were validated in a
490 population who received intensive and effective induction and consolidation therapies
491 including the second-generation PI carfilzomib with or without IMiD agents and ASCT
492 intensification. In this context, the S-ERMM maintained its prognostic role, but the
493 percentage of patients experiencing ER was definitely lower than that reported in the
494 training set.
495 In conclusion, we were able to correctly classify a good proportion of patients who
496 experienced early relapse by assessing the S-ERMM score at baseline and re-modulating
497 patient risk at 9 months with the DS-ERMM score. An external validation of the S-ERMM
498 and DS-ERMM scores is warranted, especially in patients treated with combinations of PIs,
499 IMiD agents, and anti-CD38 monoclonal antibodies. Our ability to predict ER could also be
500 improved by the inclusion of other risk features at baseline with known prognostic impact,
501 such as amp(1q21), TP53 mutational status, and circulating plasma cells (27,32,33).
502 Unfortunately, these data were not available for this analysis.
503 The correct identification of patient risk at diagnosis and during therapy is an essential
504 step towards a risk-adapted approach, the cure of patients, and the prevention of over- and
505 under-treatment.
506

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6 Tables

Table 1. Patient characteristics of the overall population, stratified according to the ER18 outcome as training set and validation set

	POOLED-SET	TRAINING SET*				VALIDATION SET*			
	Overall population	Overall population	ER18 population	Reference population	p	Overall population	ER18 population	Reference population	p
N of patients (%)	2190	844	312 (37)	532 (63)	-	374	61 (16)	313 (84)	-
Age, y Median [IQR]	63.0 [56.0, 72.0]	66.0, [57.0-73.0]	68.0 [58.0, 75.0]	65.0 [57.0, 73.0]	0.026	57.0 [51.0, 62.0]	56.0 [48.0, 62.0]	58.0 [52.0, 62.0]	0.173
Missing N (%)	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
Albumin, g/dL: Median [IQR]	3.8 [3.4, 4.2]	3.8, [3.4-4.2]	3.7 [3.2, 4.1]	3.9 [3.5, 4.2]	<0.001	3.9 [3.5, 4.3]	3.7 [3.4, 4.1]	3.9 [3.5, 4.3]	0.046
Missing N (%)	10 (0.5)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
β2m, mg/dL: Median [IQR]	3.4 [2.4, 5.1]	3.6, [2.5-5.4]	4.1 [2.8, 6.1]	3.3 [2.4, 5.0]	<0.001	2.9 [2.0, 4.2]	3.7 [2.2, 5.8]	2.8 [2, 4]	0.015
Missing N (%)	8 (0.4)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
LDH>ULN, N (%)	211 (9.6)	83 (10)	45 (14)	38 (7)	0.001	54 (14)	17 (28)	37 (12)	0.002
Missing N (%)	267 (12.2)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
del17p: N (%)	246 (11.2)	121 (14)	59 (19)	62 (12)	0.005	52 (14)	11 (18)	41 (13)	0.414
Missing N (%)	477 (21.8)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
t(4;14): N (%)	228 (10.4)	117 (14)	63 (20)	54 (10)	<0.001	57 (15)	17 (28)	40 (13)	0.005
Missing N (%)	482 (22.0)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
t(11;14): N (%)	341 (15.5)	156 (18)	50 (16)	106 (20)	0.188	87 (23)	14 (23)	73 (23)	1
Missing N (%)	522 (23.8)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
t(14;16): N (%)	78 (3.6)	32 (4)	16 (5)	16 (3)	0.171	19 (5)	4 (7)	15 (5)	0.798
Missing N (%)	506 (23.1)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
R-ISS, II/III: N (%)	1388 (63.5)	613 (73)	255 (82)	358 (67)	<0.001	250 (67)	53 (87)	197 (63)	<0.001
Missing N (%)	388 (17.7)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	

Creatinine, mg/dL: Median [IQR]	0.9 [0.7, 1.1]	0.9 [0.8-1.2]	1.0 [0.8, 1.2]	0.9 [0.8, 1.1]	0.136	0.8 [0.7, 1.0]	0.8 [0.7, 1.2]	0.8 [0.7, 1.0]	0.427
Missing N (%)	67 (3.1)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
BMPCs, >60% N (%)	612 (28)	243 (29)	112 (36)	131 (25)	0.001	139 (37)	27 (44)	112 (36)	0.267
Missing N (%)	121 (5.5)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
FLC, λ: N (%)	727 (36)	301 (36)	123 (39)	178 (33)	0.095	143 (38)	18 (30)	125 (40)	0.165
Missing N (%)	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
M component, IgA: N (%)	451 (21)	186 (22)	65 (21)	121 (23)	0.575	57 (15)	10 (16)	47 (15)	0.937
Missing N (%)	3 (0.1)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
Plasmacytomas, N (%)	266 (12)	78 (9)	27 (9)	51 (10)	0.743	49 (13)	10 (16)	39 (12)	0.532
Missing N (%)	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	

**Patients with complete data only*.

Abbreviations. N, number; y, years; ER, early relapse within 18 months from diagnosis; IQR, interquartile range; β2m, β 2-microglobulin; LDH, lactate dehydrogenase; ULN, upper limit of normal; del17p, deletion 17p; t, translocation; R-ISS, Revised International Staging System; BMPCs, bone marrow plasma cells; FLC, free light chains; M, monoclonal.

Table 2. Univariate (UV) and multivariate (MV) analyses of the baseline features to predict ER18

	ER18*					
	Analysis including R-ISS			Analysis including single features		
	UV Analysis	MV Analysis		UV Analysis	MV Analysis	
	p	OR (95% CI)	p	p	OR (95% CI)	p
Age, (increased by 1 y)	0.026	1.01 (1.00 - 1.02)	0.113	0.026	1.01 (1.00 - 1.03)	0.094
Albumin, (increased by 1 mg/dL)				<0.001	0.75 (0.60 - 0.95)	0.015
β2m, (increased by 1 mg/dL)				<0.001	-	-
LDH (> vs. ≤ULN)				0.001	2.03 (1.27 - 3.26)	0.003
del17p (presence vs. no)				0.005	1.65 (1.10 - 2.47)	0.016
t(4;14) (presence vs. no)				<0.001	2.12 (1.40 - 3.19)	<0.001
R-ISS (II/III vs. I)	<0.001	1.91 (1.35 - 2.71)	<0.001			
BMPCs % (increased by 5%)	<0.001	1.05 (1.02 - 1.08)	<0.001	<0.001	1.06 (1.03 - 1.09)	<0.001
FLC (λ vs. κ)	0.095	-	-	0.095	1.31 (0.97 - 1.78)	0.076

** Only significant features (p<0.1) in UV analysis and age were included.*
- Excluded before the MV analysis by the Akaike information criterion (AIC).
Abbreviations. ER18, early relapse within 18 months from diagnosis, R-ISS Revised International Staging System; UV, univariate; MV, multivariate; OR, odds ratio; CI, confidence interval; β2m, β 2-microglobulin; LDH, lactate dehydrogenase; ULN, upper limit of normal; del17p, deletion 17p; t, translocation; R-ISS, Revised International Staging System; BMPCs, bone marrow plasma cells; FLC, free light chains; M, monoclonal.

7 Figures: titles and legends

Figure 1. Flowchart of the S-ERMM score construction

Abbreviations. ER, early relapse; features, features; BMPCs, bone marrow plasma cells; LDH, lactate dehydrogenase; ULN, upper limit of normal; del17p, deletion 17p; t, translocation; FLC, free light chains; alb, albumin; Low, low; Int, intermediate; High, high; coeff., coefficient; OR, odds ratio; CI, confidence interval; p, p-value; S-ERMM, Simplified Early Relapse in Multiple Myeloma score.

Figure 2. OS (A) and PFS2 (B) stratified by S-ERMM score

A) OS: S-ERMM Int vs. S-ERMM Low, S-ERMM High vs. S-ERMM Low and S-ERMM High vs. S-ERMM Int.
B) PFS2: S-ERMM Int vs. S-ERMM Low, S-ERMM High vs. S-ERMM Low and S-ERMM High vs. S-ERMM Int.

Abbreviations. OS, overall survival; PFS2, progression free survival-2; S-ERMM, Simplified Early Relapse in Multiple Myeloma score; Int, intermediate; HR, hazard ratio; CI, confidence interval; p, p-value.

Figure 3. OS (A) and PFS2 (B) according to the DS-ERMM score

Landmark analysis at 9 months, corresponding to the median time to achieve ≥VGPR.
A) OS: DS-ERMM Int vs. DS-ERMM Low, DS-ERMM High vs. DS-ERMM Low, and DS-ERMM High vs. DS-ERMM Int.
B) PFS2: DS-ERMM Int vs. DS-ERMM Low, DS-ERMM High vs. DS-ERMM Low and DS-ERMM High vs. DS-ERMM Int.

Abbreviations. OS, overall survival; PFS2, progression-free survival-2; DS-ERMM score, Dynamic Simplified Early Relapse in Multiple Myeloma score; VGPR, very good partial response; Int, intermediate; HR, hazard ratio; CI, confidence interval; p, p-value.

Figure 1

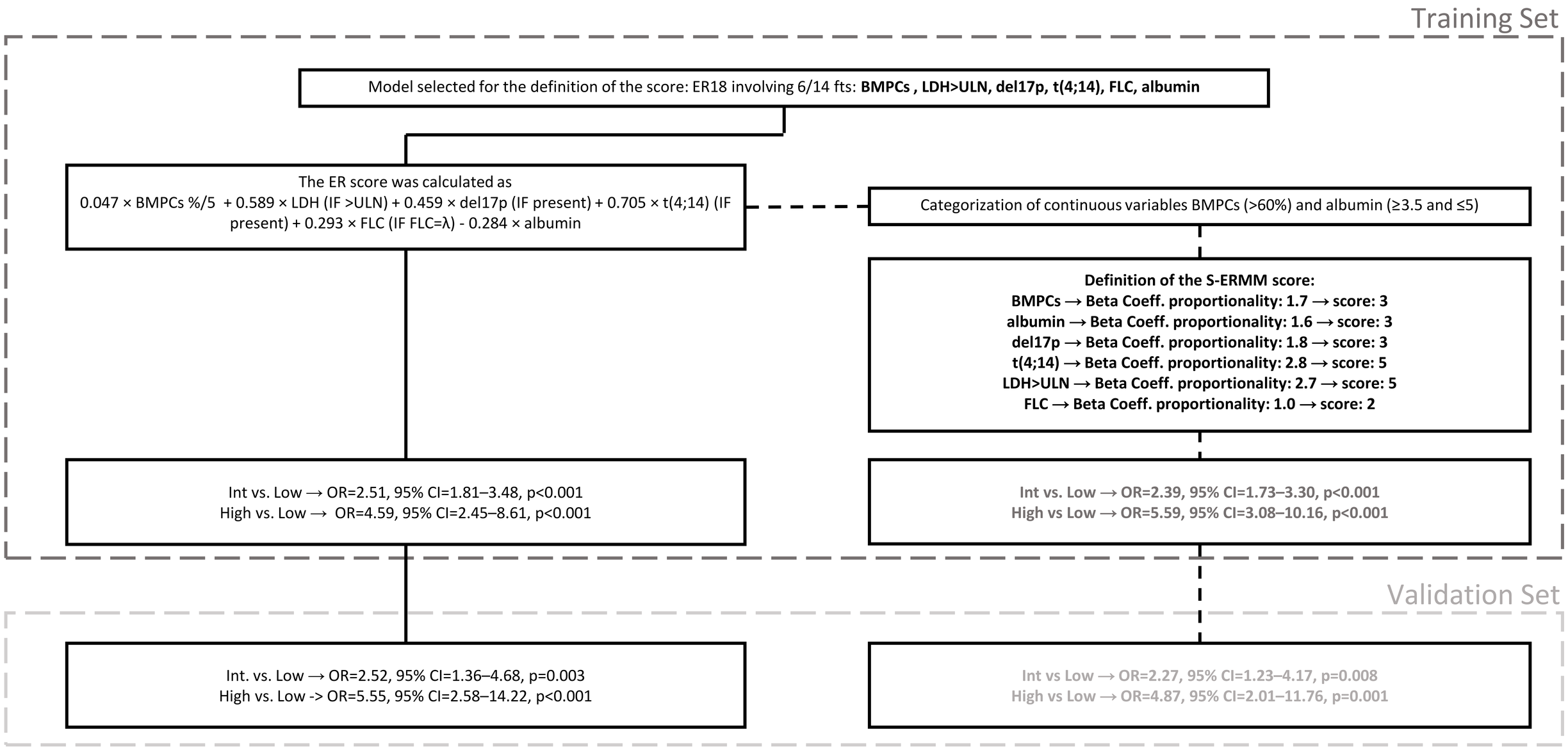
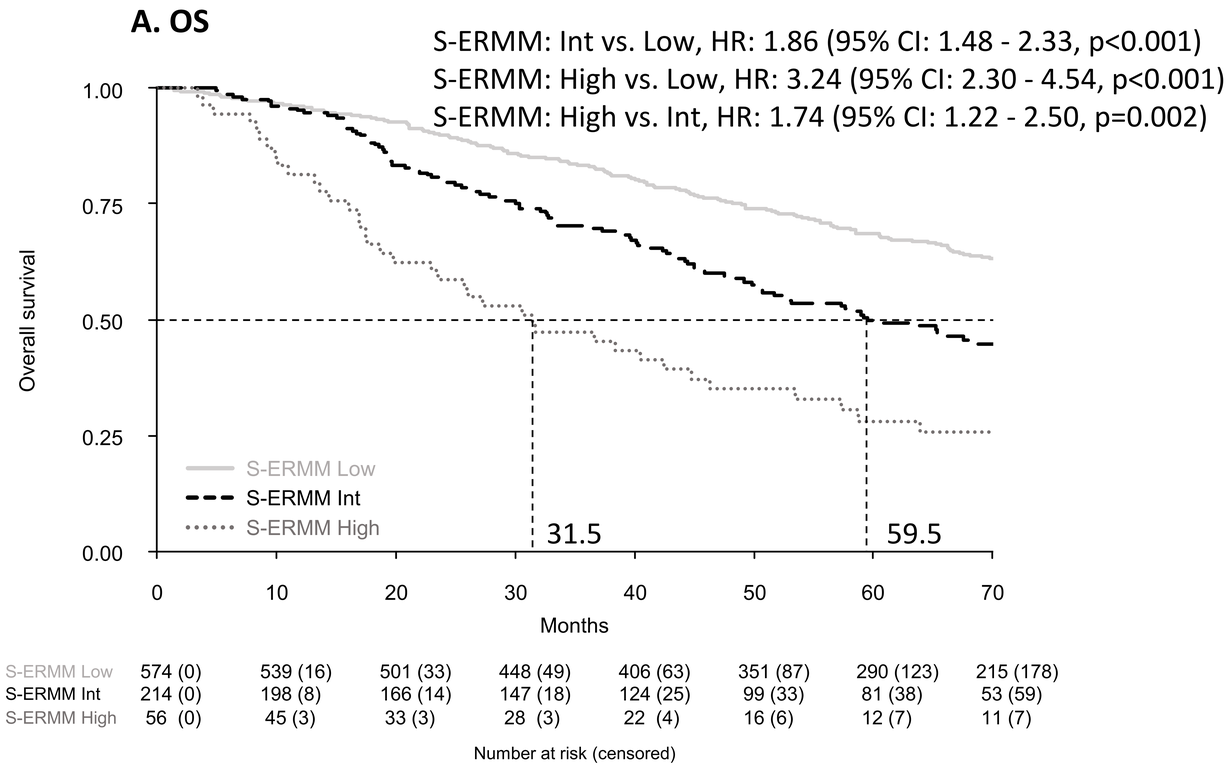

Training Set
Model selected for the definition of the score: ER18 involving 6/14 fts: **BMPCs , LDH>ULN, del17p, t(4;14), FLC, albumin**
The ER score was calculated as
0.047 × BMPCs %/5 + 0.589 × LDH (IF >ULN) + 0.459 × del17p (IF present) + 0.705 × t(4;14) (IF present) + 0.293 × FLC (IF FLC=λ) - 0.284 × albumin
Categorization of continuous variables BMPCs (>60%) and albumin (≥3.5 and ≤5)
Definition of the S-ERMM score:
BMPCs → Beta Coeff. proportionality: 1.7 → score: 3
albumin → Beta Coeff. proportionality: 1.6 → score: 3
del17p → Beta Coeff. proportionality: 1.8 → score: 3
t(4;14) → Beta Coeff. proportionality: 2.8 → score: 5
LDH>ULN → Beta Coeff. proportionality: 2.7 → score: 5
FLC → Beta Coeff. proportionality: 1.0 → score: 2
Int vs. Low → OR=2.51, 95% CI=1.81–3.48, p<0.001
High vs. Low → OR=4.59, 95% CI=2.45–8.61, p<0.001
Int vs. Low → OR=2.39, 95% CI=1.73–3.30, p<0.001
High vs Low → OR=5.59, 95% CI=3.08–10.16, p<0.001
Validation Set
Int. vs. Low → OR=2.52, 95% CI=1.36–4.68, p=0.003
High vs. Low -> OR=5.55, 95% CI=2.58–14.22, p<0.001
Int vs Low → OR=2.27, 95% CI=1.23–4.17, p=0.008
High vs Low → OR=4.87, 95% CI=2.01–11.76, p=0.001

Figure 2


A. OS
S-ERMM: Int vs. Low, HR: 1.86 (95% CI: 1.48 - 2.33, p<0.001)
S-ERMM: High vs. Low, HR: 3.24 (95% CI: 2.30 - 4.54, p<0.001)
S-ERMM: High vs. Int, HR: 1.74 (95% CI: 1.22 - 2.50, p=0.002)
Overall survival
1.00
0.75
0.50
0.25
0.00
S-ERMM Low
S-ERMM Int
S-ERMM High
31.5
59.5
0
10
20
30
40
50
60
70
Months
S-ERMM Low 574 (0) 539 (16) 501 (33) 448 (49) 406 (63) 351 (87) 290 (123) 215 (178)
S-ERMM Int 214 (0) 198 (8) 166 (14) 147 (18) 124 (25) 99 (33) 81 (38) 53 (59)
S-ERMM High 56 (0) 45 (3) 33 (3) 28 (3) 22 (4) 16 (6) 12 (7) 11 (7)
Number at risk (censored)

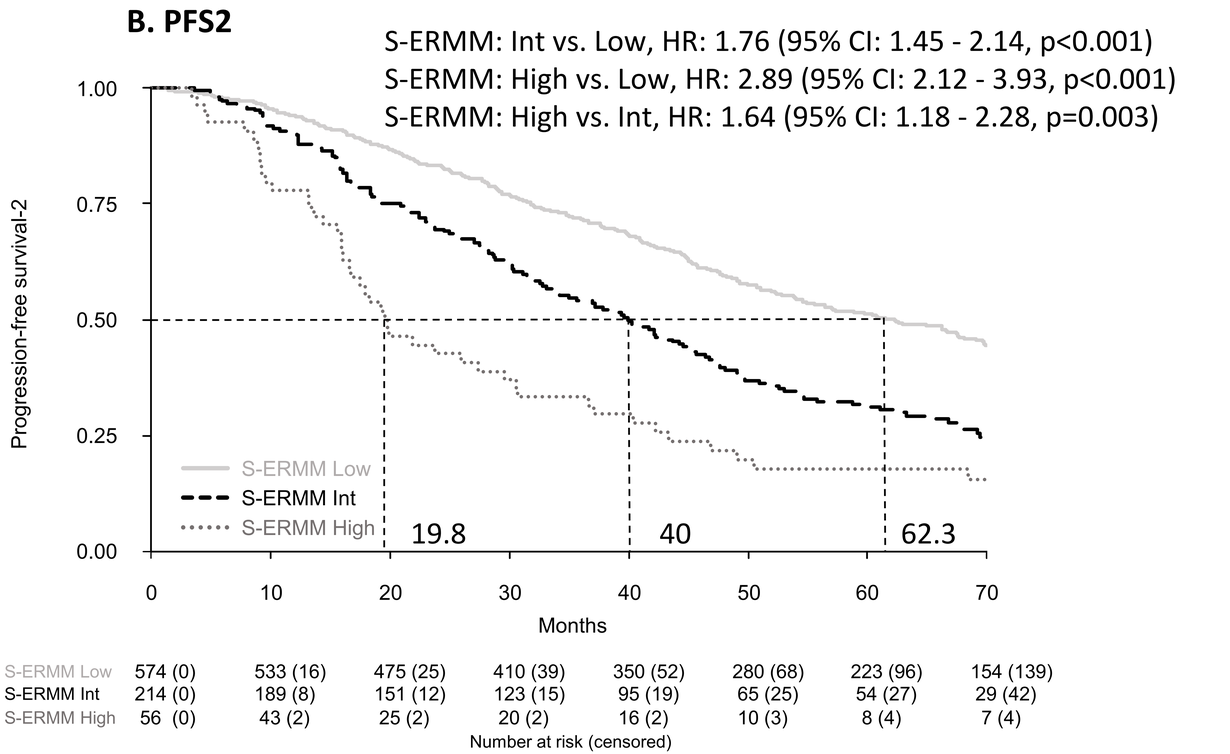
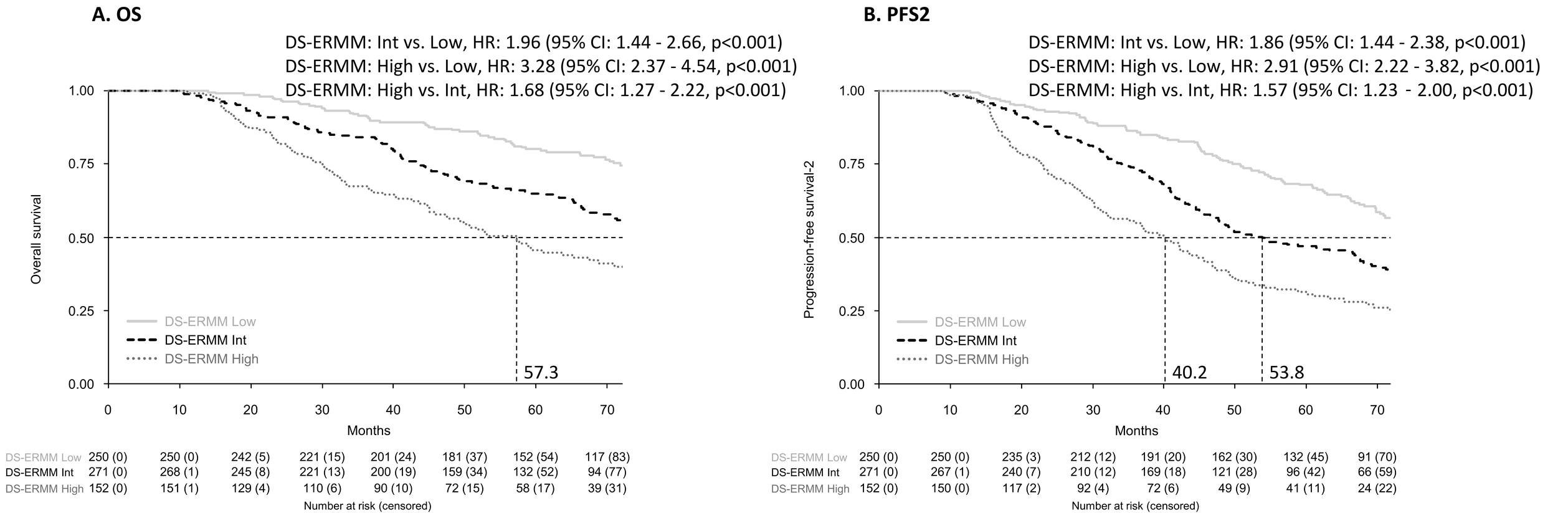

B. PFS2
S-ERMM: Int vs. Low, HR: 1.76 (95% CI: 1.45 - 2.14, p<0.001)
S-ERMM: High vs. Low, HR: 2.89 (95% CI: 2.12 - 3.93, p<0.001)
S-ERMM: High vs. Int, HR: 1.64 (95% CI: 1.18 - 2.28, p=0.003)
Progression-free survival-2
1.00
0.75
0.50
0.25
0.00
S-ERMM Low
S-ERMM Int
S-ERMM High
19.8
40
62.3
0
10
20
30
40
50
60
70
Months
S-ERMM Low 574 (0) 533 (16) 475 (25) 410 (39) 350 (52) 280 (68) 223 (96) 154 (139)
S-ERMM Int 214 (0) 189 (8) 151 (12) 123 (15) 95 (19) 65 (25) 54 (27) 29 (42)
S-ERMM High 56 (0) 43 (2) 25 (2) 20 (2) 16 (2) 10 (3) 8 (4) 7 (4)
Number at risk (censored)

Figure 3


A. OS
DS-ERMM: Int vs. Low, HR: 1.96 (95% CI: 1.44 - 2.66, p<0.001)
DS-ERMM: High vs. Low, HR: 3.28 (95% CI: 2.37 - 4.54, p<0.001)
DS-ERMM: High vs. Int, HR: 1.68 (95% CI: 1.27 - 2.22, p<0.001)
Overall survival
1.00
0.75
0.50
0.25
0.00
DS-ERMM Low
DS-ERMM Int
DS-ERMM High
57.3
0 10 20 30 40 50 60 70
Months
DS-ERMM Low 250 (0) 250 (0) 242 (5) 221 (15) 201 (24) 181 (37) 152 (54) 117 (83)
DS-ERMM Int 271 (0) 268 (1) 245 (8) 221 (13) 200 (19) 159 (34) 132 (52) 94 (77)
DS-ERMM High 152 (0) 151 (1) 129 (4) 110 (6) 90 (10) 72 (15) 58 (17) 39 (31)
Number at risk (censored)
B. PFS2
DS-ERMM: Int vs. Low, HR: 1.86 (95% CI: 1.44 - 2.38, p<0.001)
DS-ERMM: High vs. Low, HR: 2.91 (95% CI: 2.22 - 3.82, p<0.001)
DS-ERMM: High vs. Int, HR: 1.57 (95% CI: 1.23 - 2.00, p<0.001)
Progression-free survival-2
1.00
0.75
0.50
0.25
0.00
DS-ERMM Low
DS-ERMM Int
DS-ERMM High
40.2
53.8
0 10 20 30 40 50 60 70
Months
DS-ERMM Low 250 (0) 250 (0) 235 (3) 212 (12) 191 (20) 162 (30) 132 (45) 91 (70)
DS-ERMM Int 271 (0) 267 (1) 240 (7) 210 (12) 169 (18) 121 (28) 96 (42) 66 (59)
DS-ERMM High 152 (0) 150 (0) 117 (2) 92 (4) 72 (6) 49 (9) 41 (11) 24 (22)
Number at risk (censored)