An objective assessment in newly diagnosed multiple myeloma to avoid treatment complications and strengthen therapy adherence

by Maximilian Holler, Gabriele Ihorst, Heike Reinhardt, Amelie Rösner, Magdalena Braun, Mandy-Deborah Möller, Esther Dreyling, Katja Schoeller, Sophia Scheubeck, Ralph Wäsch, and Monika Engelhardt. Collaborative Groups: German Myeloma study groups (GMMG & DSMM) (Hartmut Goldschmidt / Hermann Einsele)

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Original article

An objective assessment in newly diagnosed multiple myeloma to avoid treatment complications and strengthen therapy adherence

Running title: Minimizing treatment complications in NDMM

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Abstract
In heterogeneous multiple myeloma (MM) patients treatment decisions are challenging. The hypothesis was that adaptation of treatment intensity (dose reduction [DR] vs. none) according to an objective risk score (Revised-Myeloma Comorbidity Index [R-MCI]) rather than physician judgement alone may improve therapy efficacy and avoid toxicities.

We performed this study in 250 consecutive MM patients who underwent a prospective fitness assessment at our center, yet received induction protocols based on physicians’ judgement. DR, serious adverse events (SAEs), response, progression free- (PFS) and overall survival (OS) were compared in fitness (fit, intermediate-fit, frail), age (<60, ≥70 years [y]) and therapy intensity subgroups at baseline and follow-up.

Fit and <60y patients were mostly treated with full intensity, whereas frail and ≥70y patients usually received DR. Hematological and non-hematological SAEs were more frequently seen in frail vs. ≥70y patients. Dose adaptations were mainly necessary in frail patients. OS and PFS were similar in fit and intermediate-fit but significantly worse in frail patients (p=0.0245/ p<0.0001), whereas in age-based subgroups, OS- and PFS-differences did not reach significance (p=0.1362/ p=0.0569). Non-hematological SAEs were another negative predictor for impaired OS and PFS (p=0.0054/ p=0.0021). In the follow-up performed at a median of 11 months after the first fitness assessment, the R-MCI improved or remained stable in 90% vs. deteriorated in only 10% of patients.

In conclusion, separation by R-MCI/frailty-defined subgroups was superior to age-based subgroups and can be used to improve tailored treatment. Fitter patients benefit from intensive therapies, whereas frail patients bear a need for initial DR.

Introduction
Multiple Myeloma (MM) is a hematological disease, which typically affects elderly patients.\(^1\) In the past decade, treatment options have substantially evolved and with inclusion of proteasome inhibitors (PI), immunomodulatory drugs (IMiDs) and antibodies (Ab)/immunotherapies into induction and relapse protocols, response rates, progression-free survival (PFS) and overall survival (OS) have improved impressively.\(^2\) Standard treatment in newly diagnosed MM (NDMM) includes triplets or quadruplets, plus - if patients are deemed fit enough - autologous stem cell transplantation (ASCT), followed by maintenance therapy.\(^3,4\) Albeit patient assessment, via age, Karnofsky Performance Status (KPS), comorbidities, patient-history and –examination, is performed, MM patients’ actual constitution and fitness can be over- or underestimated.\(^5-8\) Additionally, inclusion in clinical trials is especially rare in elderly patients over the age of 70 years.\(^5,6\) This suggests that more objective tools may
assist physicians to find most suitable treatment regimens and to adapt dose intensity for elderly and/or MM-stricken patients.

In line, the long continuing COVID-19 pandemic imposes the need to prevent any unnecessary serious adverse events (SAEs), hospitalization, time-consuming dose adjustments and therapy cessations. However, therapy decisions are often made without an objective fitness assessment yet. In recent years, MM-specific risk scores (e.g. International Myeloma Working Group (IMWG)-frailty score, Revised-Myeloma Comorbidity Index (R-MCI), Mayo-risk score, UK Myeloma Research Alliance Risk Profile) were developed to assist in this unsolved matter.

The hypothesis of this study was that adaptation of therapy intensity according to an objective risk score (via R-MCI; Figure S1), rather than via physician judgement alone, may improve therapy-efficacy and avoid -toxicities and –discontinuation. More studies are now testing the feasibility of MM-specific risk-scores for treatment assistance in MM patients, albeit additional studies should further be performed. We used the R-MCI, because this constitutes a repeatedly validated MM-specific risk tool, used routinely for MM patients at our institution, that has been integrated into our electronic tumorboard (TB) online system. The R-MCI contains of 5 weighted risk factors, namely renal and lung function, KPS, frailty and age, plus allows to include cytogenetics. The R-MCI web tool allows the immediate calculation of the weighted R-MCI, which can be likewise performed by physicians or research assistants (www.myelomacomorbidityindex.org). We here investigated the applicability of the R-MCI for future therapy decision support by performing an analysis on patients receiving first-line treatment. Main aspects of this study were to track patients’ induction treatment, comparing R-MCI- vs. age-subgroups in terms of therapy adaptations, SAEs, response, OS and PFS.

Since patients’ constitution and disease burden may change during treatment, we also reevaluated constitution, fitness and R-MCI changes in a follow-up analysis (Figure S2).

Methods

Data sources and study design:

We performed this exploratory study in 250 consecutive MM patients, who received induction treatment ideally continuing until intolerance or progression at our Comprehensive Cancer Center Freiburg (CCCF) and catchment area of the Black Forest from 2000-2018. All patients were fully documented at our CCCF. The cohort with prospectively assessed R-MCIs was pooled from two prior conducted analyses, retrieving patient- and therapy-relevant data through our electronic documentation system ‘Medoc’. Of initial 359 patients,
109 had to be excluded either due to ongoing induction at the time of assessment (n=50) or incomplete data (n=59; Figure S2). Patients’ characteristics included the International Staging System (ISS), R-MCI and IMWG-frailty scores at baseline. Via R-MCI and IMWG-frailty scores, all patients were divided into fit, intermediate-fit or frail (Table 1 and Figure S1). Decisions of induction regimen, treatment intensity and dose reductions (DR) were based on physicians’ choice. Comparisons were performed for frailty- (R-MCI-fit, -intermediate-fit, vs. -frail), age- (<60, 60-69 vs. ≥70 years) and therapy-intensity (with vs. without initial DR) subgroups.

The study was performed according to the guidelines of the Declaration of Helsinki and Good Clinical Practice. All patients gave their written informed consent for institutionally initiated research studies and analyses of clinical outcome studies conforming to the institutional review board guidelines. The trial protocol was approved by the ethics committee of the University of Freiburg (EV 81/10).

Induction, dose reductions (DR), SAEs, response and follow-up analysis

For each induction regimen, one lead agent was determined. Albeit any DR of any drug in combination first-line treatment could have been counted as a dose modification, this would not have allowed a less complex intensity calculation. Thus, any decrease in the lead agents’ standard dose intensity or change from triplets to doublets was defined as DR. Lead agents were defined, with regard to the severity of adverse events (AEs) in the following order of priority: alkylating agents, subsequently IMiDs and PI/Ab, last anthracyclines or glucocorticoids. The standard dose was consistent with NCCN/EMN-guidelines and CCCF-chemotherapy manual.24

We used the Common Terminology Criteria (CTC) for AEs version 5.0 to assess grade 3-4 hematological SAEs (anemia, leukocytopenia, thrombocytopenia) and non-hematological SAEs grades 3-5 (infections, renal, pulmonary, cardiac impairment).

Quality of response was assessed via IMWG-remission criteria until the end of induction.25,26 Six to 24 months after the first fitness assessment, we analyzed, if changes in remission status and patients’ constitution via a follow-up R-MCI analysis had occurred.

Statistical analysis:

OS was defined as the time from start of induction to death from any cause and PFS as the time from start of induction to cancer recurrence or death from any cause. Data for patients alive at the time of the analysis were censored at the last follow-up. Probabilities of PFS and OS were estimated using Kaplan-Meier method and compared with logrank tests. To avoid an immortal time bias, plots of OS and PFS of patients showing no or at least one SAE, included only those who survived at least six months after the start of induction treatment.
Chi-square- and Mantel-Haenszel tests were utilized as appropriate in the comparisons of therapy protocols, DR, SAEs, response rates in R-MCI and age groups. A $P$ value of $<0.05$ was considered as statistically significant. Data were analyzed with SAS 9.2 (SAS Institute, Inc, Cary, North Carolina).

Results

Patient characteristics' and induction regimen

Among the 250 analyzed patients the median age at baseline was 62 years and 61% were males. For a cohort, where first-line treatment was mainly applied at a tertiary and referral center, patient characteristics were typical (Table 1), likewise myeloma subtypes, ISS, median bone marrow infiltration (45%) underlying AL-amyloidosis rate (6%), and cytogenetics. ISS stage 2 and 3 were most common with 66% (Table 1).

Median IMWG-frailty score and R-MCI were 1 and 4, respectively, in line with prior test and validation analyses.\textsuperscript{15,17,23,27,28} Impaired constitution via KPS $\leq 70\%$ was present in 42% and moderate or severe frailty was reported in 36%.\textsuperscript{8,17,23} Renal impairment with eGFR $<60\text{mL/min/1.73m}^2$ was present in 40% and moderate or severe lung dysfunction as defined via R-MCI website in 12%, in line with previous analyses.\textsuperscript{8,17,23,29,30}

VCD, VRd/RAD or other induction (Figure S3) was predominantly performed with VCD and whenever possible in German study group (DSMM)-protocols (DSMM XI, XII, XIV).\textsuperscript{31,32} Induction was often initiated at the CCCF, but also at regional hospitals and private practices. Stem cell transplantation (SCT) was performed in 72% (Table 1).

Comparisons of patient and therapy relevant parameters in entire cohort, and in R-MCI-, age- and dose-intensity subgroups

Patient and therapy parameters are summarized in Table 2 in entire cohort and in fit vs. frail, younger vs. older and full-dosed (no DR) and dose reduced (initial DR) subgroups. No initial DR vs. DR were performed in 59% and 41%, respectively, reflecting the complexity to treat an even fairly young MM cohort, and that initial DR was frequently performed. Number of hematological and non-hematological SAEs were frequent with 157 and 123, which accounted for SAEs per patient in 0.63 and 0.49, respectively. The median induction duration was 62 days. Best IMWG response ($\geq PR$) after induction was observed in 75% in line with prior data (Table 2).\textsuperscript{31}

Results of R-MCI fit and younger (<60 years) patients were similar and merely differed in used protocols and SAEs (Table 2). Intermediate-fit and frail patients (combined: 71%) showed increased median ages of 66 and 74 years, respectively. VRd/RAD first-line
treatment in fit, intermediate-fit and frail patients were performed in 37%, 15% and 6%, thus decreased with frailty, whereas DR substantially increased (19%, 45%, 72%, respectively; Table 2).

In line, SAEs per patient increased from 0.23 in fit, to 0.72 in intermediate-fit and 1.1 in frail patients for hematological SAEs, and 0.23, 0.48 and 1.13 for non-hematological SAEs. Median induction duration in intermediate-fit patients was similar to fit patients, basically because SCTs in intermediate-fit patients remained considerable with 72%. Expectedly, in frail patients longer induction (6-9 cycles plus maintenance) was performed and less SCTs (Table 2).

Divided into fit, intermediate-fit and frail patients, the response rates were 73%, 77% and 69%, respectively, thus higher in both former than latter subgroup (Table 2).

According to age subgroups, DR increased in <60, 60-69 and ≥70-year-old patients from 21% to 43% and 66%, respectively. SAEs per patients increased lesser and seemed less predictable than in R-MCI subgroups (Table 2). Transplant eligible patients aged 60-69 years did hardly show differences in non-hematological SAEs compared to patients ≥70 years (0.58/patient vs. 0.62/patient). SCT frequencies were typical in young in 93%, 81% in 60-69 and 32% in ≥70-year-old patients. Transplant-ineligible patients (≥70 years) were at treatment initiation in 29/73 (40%) >75 years old. Best responses (≥PR) in age cohorts ranged from 66-79% (Table 2).

In dose intensity subgroups, for patients without vs. with DR, median age- and R-MCI-differences were notable with 58 vs. 69 years and 4 vs. 5, respectively. This was in line with lesser performed SCTs in the latter group (Table 2). Whereas hematological SAEs/patient were similar in patients without vs. with DR, these almost doubled for non-hematological SAEs (0.36 vs. 0.69/patient, respectively). Median induction duration was similar in both groups, while expectedly, response rates (≥PR) were increased in patients without DR (Table 2).

**SAEs: subgroup distribution for hematological and non-hematological SAEs**

Distinct differences in types of hematological and non-hematological SAEs are shown in Figure 1A and B, being more prevalent in frail than intermediate-fit or fit patients.

Anemia, leukocytopenia and thrombocytopenia SAEs (CTC grade 3-4) occurred in 76, 56 and 25 patients, respectively. Leukocytopenia was equally prevalent in frail and intermediate-fit patients (44% and 45%, respectively), while anemia and thrombocytopenia were predominantly observed in frail patients (59% and 68%, respectively; Figure 1A).

Hematological SAEs appeared in patients treated with alkylating agents (VCD) in 47% and with IMID-based protocols (VRd/RAD) in 20% (‘others’ were too few for meaningful conclusions).
Of 123 registered non-hematological SAEs, 69 were attributed to infectious, 23 to renal, 18 to pulmonary and 13 to cardiac causes (Figure 1B). Comparison of different R-MCI subgroups with infectious, renal, pulmonary and cardiac SAEs showed significant increases in frail as compared to fit or intermediate-fit patients, reaching significance in all except pulmonary SAEs (Figure 1B).

**Therapy adaptations in frailty- and age subgroups**

Our assessment of SAEs in patients without or with initial DR is depicted in Table S1A and B. The occurrence of hematological SAEs without or with DR did not show distinct differences in frailty subgroups. Therapy adaptations (DR, therapy pauses or discontinuation) after hematological SAEs occurred in intermediate-fit or frail patients only, both without and with performed initial DR (Table S1A). Non-hematological SAEs occurred in R-MCI subgroups likewise more often in patients without DR than if performed, whereas this was less strikingly found for age subgroups (Table S1B). Therapy adjustments or discontinuations after non-hematological SAEs increased both with frailty and age, and were more prevalent with full doses than if DR had been performed (Table S1B).

Therapy discontinuation occurred in only 8/250 (3%) patients (Table S2), showing mostly advanced ages and impaired R-MCI scores. Initial dose reductions had been performed in 7/8. Patient constitution-, myeloma- and/or therapy-induced complications occurred in already the 1st (n=3) to 4th (n=3) induction cycle (range 1-4). Retrospectively assessed therapy intensity by us (MH, ME) suggested in 7/8, that these were overdosed. Thus, if on top of clinical judgement, R-MCI-tailored therapy had been performed - SAEs and therapy cessation might have been avoided in 7/8 patients.

**SAEs leading to early death (<60 days after induction) or concomitant SAEs**

SAEs during induction which led to death were seen in three patients (3/250=1.2%). These showed cardiac complications, 2 out of 3 associated with underlying AL-amyloidosis. Sixteen patients with concomitant AL-amyloidosis contributed to 28% of cardiac (n=13) and renal (n=23) SAEs (CTC 3-5) of the entire cohort, thus showed a 5.6 higher risk for these complications. Expectedly, patients with CTC grade 3-4 leukocytopenia were more likely to acquire severe infections (Table S3).

**OS and PFS of entire cohort and in various subgroups**

The median follow-up from start of induction was 65 months (range: 1-246). Detailed responses in fit, intermediate-fit and frail patients are summarized in Table S4. The Kaplan-Meier curves for OS and PFS analyses are displayed in Figure 2 and 3. The estimated 3-
year OS and PFS in the entire cohort were 85% (95%CI: 79-89%) and 53% (95%CI: 47-60%), respectively (Figure 2A and B). The three R-MCI subgroups in Figure 2C and D showed similar results for both fit and intermediate-fit patients. The 3-year OS in R-MCI fit, intermediate-fit and frail was 89% (95%CI: 79-94%), 85% (95%CI: 77-90%) and 70% (95%CI: 47-85%), respectively (p=0.0688; Figure 2C). The 3-year PFS was 60% (95%CI: 47-70%), 55% (95%CI: 47-63%) and 21% (95%CI: 6-41%), respectively (p<0.0001; Figure 2D). Since results of fit and intermediate-fit patients were comparable and much different to frail patients, these were combined as displayed in Figure 2E and F. Of note, 3-year OS and PFS in fit/intermediate vs. frail patients showed highly significant differences of 86% (95%CI: 81-90%) vs. 70% (95%CI: 47-85%) and 57% (95%CI: 50-63%) vs. 21% (95%CI: 6-41%), respectively (p=0.0245/p<0.0001).

Age subgroups revealed differences with best OS/PFS for <60-year old patients, whereas 60-69 and ≥70-year subgroups revealed similar Kaplan Meier curves. Notably, 3-year OS/PFS results via age displayed lesser and insignificant group distinctions (p=0.1362/p=0.0569; Figure 2G and H).

**SAEs and DR impact on OS and PFS**

Any SAE led to impaired OS and PFS (Figure 3A and B), both for hematological (Figure 3C and D) and non-hematological SAEs (Figure 3E and F), with more striking OS and PFS differences for the latter SAEs. In line, DR vs. no DR led to both OS and PFS differences in favor of patients with no DR, reflecting standard doses to be easier applied in fitter and younger patients and therefore accounting for these differences (Figure 3G and H).

**R-MCI follow-up analysis**

The follow-up analysis (T0 → T1) was possible in 180 patients (72%; Figure 4 and S2). The median follow-up was 11 months (range 6-24), in line with our previous study. Median R-MCI scores at T0 and T1 were both 4, reflecting intermediate-fit patients. Assessing also mean T0 vs. T1 differences, the R-MCI improved from 4.3 to 3.7, respectively and accounted for a mean improvement of 0.6 points over an 11 month period (p<0.0001). Among all follow-up patients, 77 (43%) achieved a better, 84 (47%) a stable and only 19 (10%) a worse R-MCI (Figure 4). Maximum R-MCI changes were improvements of four points (R-MCI 6 → 2) and deteriorations of three points (R-MCI 4 → 7), impressively illustrating that R-MCI changes within a ~1 year follow-up can be more drastic than age shifts within this period.
Discussion
One crucial aspect for MM patients and physicians is the individual selection of the initial (and subsequent) treatment and its intensity.\textsuperscript{7,33} Our message was that we are applying evidence generated from clinical trials that rarely include old or frail patients to treat such patients without knowing about the need for modifications of the used drugs, dosing or schedule. Although our study population received first-line MM treatment with dose modifications according to best clinical judgement and a prospective frailty assessment was performed, the frailty assessment was not used for decision making. Thus clinicians were blinded to this information. This allowed to assign patients into those without vs. with DR as compared to comorbidity and age subgroups (Table 2). Hence, we investigated physicians’ therapy decisions in a NDMM population during induction by analyzing the course of therapy and patient outcome. Our data demonstrated that the use of the R-MCI can assist to anticipate the likelihood of SAEs. Those predictions can subsequently be used to optimize induction dose intensity (Table 2; Figure 1A and B) and identify patients at risk of treatment discontinuation with the associated risk of a more unfavorable outcome (Figure 2 and 3). We found compelling differences between R-MCI subgroups regarding protocols and doses prescribed. Overall, alkylating agents were the mostly used lead agent, in line with VCD being a commonly applied DSMM/GMMG and EMN-study regimen.\textsuperscript{31,34} With a median start of induction in 2016, most frail patients in our cohort were guideline-compliantly treated with dose-adjusted VCD or Vd as first-line treatment.\textsuperscript{34} The EHA-ESMO guideline from 2021 propagates now to add a CD38-antibody (e.g. Dara-VMP, Dara-Rd) in NDMM patients ineligible for ASCT, reiterating that R-MCI- or other risk-tool-adapted triplets and quadruplets may profit from our here described approach to avoid SAEs and therapy cessations.\textsuperscript{33} We were also able to show that patients at risk were mostly identified correctly and reasonable dose adaptations were made, but potential improvements did remain. Moreover, we determined that fit patients had few initial DR (19%) and a low incidence of hematological or non-hematological SAEs (both 0.14 per patient). In contrary, full-dosed frail patients (28%) were nine times more likely to suffer from hematological SAEs and had a four times higher rate of non-hematological SAEs (Table S1A+B). The conjecture that some frail patients were possibly overtreated and dose-reduced fit patients undertreated is therefore plausible and has been described previously.\textsuperscript{6,17,23,34} Besides, the 3-year OS was superior in frail patients with initial DR vs. in frail patients without initial DR (73% vs. 63%). Although numbers of this subgroup comparison were limited, other studies confirm this observation.\textsuperscript{11,22,35,36} Moreover, we observed that two of three events of death were associated with subclinically underlying AL-amyloidosis. These findings confirmed the need to critically evaluate induction protocols and doses to avoid therapy complications and to reliably detect AL-amyloidosis.\textsuperscript{37,38} Indeed,
the occurrence of any SAE was associated with a worse outcome (Figure 3A), validating prior studies.\textsuperscript{11,36,37}

Since various treatment pathways continue to suggest age-cut-offs (i.e. >60 or >70-years), we divided our cohort into those <60, 60-69 and ≥70 years and compared them to R-MCI and therapy intensity (DR vs. no DR performed) subgroups (Table 2). In line with our and other prior analyses, R-MCI subgroups differed exceedingly more than age or dose intensity-subgroups, supporting the paradigm of an objective, functional GA and risk score.\textsuperscript{5,8,39–42} Notably, ≥70 years and 60-69-year old (transplant eligible) patients showed similar results regarding SAEs, OS and PFS and thereby differed to <60-year old patients, whereas for fitness groups, fit- and intermediate patients were comparable and much distinct to frail patients. Since patients ≥70 years are often excluded from clinical trials and more intensive therapies, we assessed this age group more thoroughly.\textsuperscript{6,34,42,43} Of interest, 32% of our ≥70-year old patients received a SCT after physicians’ appraisal (Table 2). Nevertheless, 56% (n=28) of patients ≥70 years, who did not receive a SCT, were classified as intermediate-fit or fit. Thus, those patients may have received intensive treatment. Larocca et al. elegantly demonstrated the benefit of a therapy-decision approach (dose-adjusted Rd-R vs. continuous Rd) via IMWG-frailty index in intermediate-fit patients in a prospective study.\textsuperscript{20} An ongoing, equally important Medical Research Councils study randomizes unaltered to adjusted treatment according to fitness results (FiTNEss study, NCT03720041, PI: G.Cook), both supporting our findings.

Concerning patients’ outcome, we observed a substantial OS and PFS advantage in fit and intermediate-fit vs. frail patients (Figure 2A and B). In line, Facon et al. propagated a simpler approach of the IMWG-frailty score, dividing patients likewise into non-frail vs. frail patients, which seems straightforward for clinical routine and clinical trials.\textsuperscript{21} An understandable request is that these risk-assessments should not be time-consuming and prospectively performed.\textsuperscript{7} Both, the R-MCI and IMWG-frailty index offer online tools for their automatic calculation.

Strengths of our analysis were the meticulous examination of a NDMM patient cohort, of performed treatment, doses, SAEs, PFS and OS in R-MCI, age and therapy intensity subgroups. Moreover, 72% of the initially assessed patients could be included in our follow-up analysis and their constitution and fitness, as measured via R-MCI, revealed improvement or stabilization in 90% and deterioration in only 10%. We have previously described in an even more detailed functional analysis using 12 different comorbidity scores and functional tests: the assessments more frequently and significantly changed in younger patients (<70 years) and those with good response (≥PR), suggesting a better functional reconstitution in younger and responsive than in older and less responsive myeloma patients.\textsuperscript{8} These 10% of
patients, whose R-MCI deteriorated in our follow-up analysis, should be reliably identified, because fittingly chosen therapies are relevant to perform and will ideally improve patients' quality of life (QoL). This was also reflected in frequencies of non-hematological SAEs, which were much lower in patients with improved or stable R-MCI (both 0.39/per patient) than in those with deteriorated R-MCI (0.53/per patient). No difference in infections was observed, most likely, due to the use of detailed chemotherapy treatment plans, including strict antibiotic prophylaxis schedules therein. Although OS differences between these subgroups were hampered by limited patient numbers with deteriorated R-MCI, our follow-up analysis confirmed that MM treatment may indeed improve patients' constitution. Renal impairment and/or frailty (including KPS) may recover under MM therapies, whereas in those not improving and deteriorating with QoL domains, therapeutic adjustments are important to consider. Additionally, our median observation period of 5.4 years was substantial, therefore our Kaplan Meier results in all patients, in R-MCI, age, SAE-experiencing and dose-reduced patients were robust and mature. So far, there are few studies on prospective MM-specific risk tools for therapy-decision-support for NDMM and even lesser for relapsed/refractory (RR)MM patients, albeit these data and currently ongoing GIMEMA, MRC, HOVON and other studies support these endeavors. Lastly, these data impressively confirm that the R-MCI seems superior to age-based treatment pathways.

Limitations of our study were the single institution approach, yet due to strict inclusion criteria regarding patients' and therapy data, all patients included provided infinitely detailed information. Another criticisms could be the heterogeneity in patients (age range: 27-92 years), with a considerable number of patients <70 years (71%), as is typical for tertiary centers in Germany (vs. more centralized institutions and countries). Since our university- and catchment area-treated patient population was relatively young and the majority received ASCTs, we refrained from non- vs. ASCT-based subgroup analyses, but considered all patients as one group. Besides, one could criticize the use of other than VCD-induction protocols in rare subgroups. Underlying AL-amyloidosis could also been argued to be possibly excluded, which we decided against, because all patients were initially diagnosed with MM only, but determined with AL-amyloidosis by us, thus initially remaining undetected. Lastly, we did not analyze the event free survival as shown in prior studies, as we focused on OS/PFS. The former will be part of another upcoming study at our institution.

In conclusion, our results demonstrate the higher frequency of SAEs, higher discontinuation rates and early mortality in frail patients, supporting MM patients' need for individualized induction and relapse protocols. Full-dose intensity for fit and reduced doses for frail patients appears pertinent, whereas intermediate-fit patients need continuing consideration.
The precise fitness assessment in MM, similar to other hematological malignancies, seems relevant to achieve favorable treatment results, less DRs, SAEs, as few unscheduled re-hospitalizations and preserved QoL.\textsuperscript{7,12,42,48,49} The latter demonstrated to be possible even after intensive regimens, after allogeneic transplantation or quadruplet RRMM treatment.\textsuperscript{8,17,23,27,28} The implementation of functional assessments in myeloma TBs may also support physicians in treatment decisions, since this adds an objective assessment of patients’ individual constitution and possible treatment endurance. Future studies are needed to evaluate the benefits of a functionally adapted treatment approach vs. ‘treatment as usual’. Prospective studies using the R-MCI in TBs for therapeutic decision support are in process at our CCCF.
Literature


Table 1. Baseline multiple myeloma patient characteristics (n=250)

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<td>160 / 88 / 1 / 1</td>
<td>64 / 35 / 0.5 / 0.5</td>
<td></td>
</tr>
<tr>
<td><strong>International Staging System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I / II / III</td>
<td>84 / 71 / 95</td>
<td>34 / 28 / 38</td>
<td></td>
</tr>
<tr>
<td><strong>Bone marrow infiltration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytology / histopathology (%)</td>
<td></td>
<td></td>
<td>35 / 45 (0-90 / 0-100)</td>
</tr>
<tr>
<td><strong>AL-Amyloidosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes / no</td>
<td>16 / 234</td>
<td>6 / 94</td>
<td></td>
</tr>
<tr>
<td><strong>Cytogenetics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable / unfavorable*</td>
<td>109 / 112 / 29</td>
<td>43.6 / 44.8 / 11.6</td>
<td></td>
</tr>
<tr>
<td>missing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidity indices</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMWG-frailty score: fit / interm. / frail</td>
<td>75 / 86 / 89</td>
<td>30 / 34 / 36</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>R-MCI: fit / interm. / frail</td>
<td>73 / 145 / 32</td>
<td>29 / 58 / 13</td>
<td>4 (0-9)</td>
</tr>
<tr>
<td><strong>KPS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 / 80-90 / ≤70%</td>
<td>15 / 130 / 105</td>
<td>6 / 52 / 42</td>
<td></td>
</tr>
<tr>
<td><strong>Frailty</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/mild : moderate/severe</td>
<td>160 : 90</td>
<td>64 : 36</td>
<td></td>
</tr>
<tr>
<td><strong>Renal function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR ≥90 / 89-60 / &lt;60ml/min</td>
<td>50 / 101 / 99</td>
<td>20 / 40 / 40</td>
<td></td>
</tr>
<tr>
<td><strong>Lung dysfunction</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/mild : moderate/severe</td>
<td>221 : 29</td>
<td>88 : 12</td>
<td></td>
</tr>
<tr>
<td><strong>Therapy induction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCD / VRD/RAD / other*</td>
<td>176 / 35 / 39</td>
<td>70 / 14 / 16</td>
<td></td>
</tr>
<tr>
<td>Place of induction: CCCF / others*</td>
<td>198 / 52</td>
<td>79 / 21</td>
<td></td>
</tr>
<tr>
<td>Performed SCT / non-SCT</td>
<td>179 / 71</td>
<td>72 / 28</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations:
IMWG: International Myeloma Working Group; interm.: intermediate-fit; R-MCI: Revised Myeloma Comorbidity Score; KPS: Karnofsky Performance Status; eGFR: estimated Glomerular Filtration Rate; VCD: Bortezomib, Cyclophosphamide, Dexamethasone; VRd: Bortezomib, Lenalidomide, Dexamethasone; RAD: Lenalidomide, Adriamycin, Dexamethasone; CCCF: Comprehensive Cancer Center Freiburg; SCT: Stem Cell Transplant

*1 Unfavorable: del17p13, t(4;14), t(14;16), t(14;20), chromosome 1 abnormalities, c-myc, del(13q14), hypodiploidy

*2 Frailty*: Karnofsky Index ≤70%; Time Up/Go >10 seconds; IADL ≤4 points; subjective fitness grade E or F

*3 Lung dysfunction: Mild: FEV1 <80%; moderate: FEV1 ≤60% or diffusion capacity ≤61%; severe: FEV1 <50%; mild: 0/1 parameter is correct; moderate: 2 parameters are correct; severe: >2 parameters are correct

*4 Others: Proteasome inhibitors, antibodies, anthracyclines, glucocorticoids

*5 Others: Regional hospitals/private practices
Table 2. Patient and therapy parameters in entire cohort, in R-MCI-, age and dose intensity subgroups

<table>
<thead>
<tr>
<th></th>
<th>Entire group</th>
<th>Fit</th>
<th>Intermediate</th>
<th>Frail</th>
<th>&lt;60 years</th>
<th>60-69 years</th>
<th>≥70 years</th>
<th>No initial DR</th>
<th>Initial DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>250 (100%)</td>
<td>73 (29)</td>
<td>145 (58)</td>
<td>32 (13)</td>
<td>101 (40.4)</td>
<td>76 (30.4)</td>
<td>73 (29.2)</td>
<td>148 (59)</td>
<td>102 (41)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>62 (27-92)</td>
<td>55 (29-77)</td>
<td>66 (27-85)</td>
<td>74 (61-92)</td>
<td>53 (27-59)</td>
<td>65 (60-69)</td>
<td>75 (70-92)</td>
<td>58 (29-80)</td>
<td>69 (27-92)</td>
</tr>
<tr>
<td>Median R-MCI (range)</td>
<td>4 (0-9)</td>
<td>3 (0-3)</td>
<td>5 (4-6)</td>
<td>7 (7-9)</td>
<td>3 (0-6)</td>
<td>4 (2-8)</td>
<td>6 (2-9)</td>
<td>4 (0-9)</td>
<td>5 (2-9)</td>
</tr>
<tr>
<td>Lead agents¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylating agents (%) (mainly VCD)</td>
<td>190 (76)</td>
<td>42 (57.5)</td>
<td>119 (82)</td>
<td>29 (91)</td>
<td>71 (70)</td>
<td>56 (73.7)</td>
<td>63 (86.3)</td>
<td>109 (74)</td>
<td>79 (77)</td>
</tr>
<tr>
<td>IMiDs (%) (mainly RAD/V Rd)</td>
<td>51 (20)</td>
<td>27 (37)</td>
<td>22 (15)</td>
<td>2 (6)</td>
<td>24 (24)</td>
<td>18 (23.7)</td>
<td>9 (12.3)</td>
<td>37 (25)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Others*² (%)</td>
<td>9 (4)</td>
<td>4 (5.5)</td>
<td>4 (3)</td>
<td>1 (3)</td>
<td>6 (6)</td>
<td>2 (2.6)</td>
<td>1 (1.4)</td>
<td>2 (1)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Initial dose reduction (DR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>148 (59)</td>
<td>59 (81)</td>
<td>80 (55)</td>
<td>9 (28)</td>
<td>80 (79)</td>
<td>43 (57)</td>
<td>25 (34)</td>
<td>148 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Yes (%)</td>
<td>102 (41)</td>
<td>14 (19)</td>
<td>65 (45)</td>
<td>23 (72)</td>
<td>21 (21)</td>
<td>33 (43)</td>
<td>48 (66)</td>
<td>0 (0)</td>
<td>102 (100)</td>
</tr>
<tr>
<td>Hematological SAEs (per patient)</td>
<td>157 (0.63)</td>
<td>17 (0.23)</td>
<td>105 (0.72)</td>
<td>35 (1.1)</td>
<td>54 (0.53)</td>
<td>44 (0.58)</td>
<td>59 (0.81)</td>
<td>92 (0.62)</td>
<td>65 (0.63)</td>
</tr>
<tr>
<td>Non-hematological SAEs (per patient)</td>
<td>123 (0.49)</td>
<td>17 (0.23)</td>
<td>70 (0.48)</td>
<td>36 (1.13)</td>
<td>34 (0.34)</td>
<td>44 (0.58)</td>
<td>45 (0.62)</td>
<td>53 (0.36)</td>
<td>70 (0.69)</td>
</tr>
<tr>
<td>Median induction duration (days)</td>
<td>62 (2-365)</td>
<td>61 (14-365)</td>
<td>61 (2-299)</td>
<td>80 (5-271)</td>
<td>59 (10-217)</td>
<td>62 (2-365)</td>
<td>78 (5-299)</td>
<td>61 (5-299)</td>
<td>65 (2-365)</td>
</tr>
<tr>
<td>Performed SCTs (%)</td>
<td>179 (72)</td>
<td>68 (93)</td>
<td>104 (72)</td>
<td>7 (22)</td>
<td>94 (93)</td>
<td>62 (81)</td>
<td>23 (32)</td>
<td>126 (85)</td>
<td>53 (52)</td>
</tr>
<tr>
<td>Obtained best response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/vgPR/PR (%)</td>
<td>187 (75)</td>
<td>53 (73)</td>
<td>112 (77)</td>
<td>22 (69)</td>
<td>79 (78)</td>
<td>50 (66)</td>
<td>58 (79)</td>
<td>118 (80)</td>
<td>69 (68)</td>
</tr>
<tr>
<td>SD/PD (%)</td>
<td>63 (25)</td>
<td>20 (27)</td>
<td>33 (23)</td>
<td>10 (31)</td>
<td>22 (22)</td>
<td>26 (34)</td>
<td>15 (21)</td>
<td>30 (20)</td>
<td>33 (32)</td>
</tr>
</tbody>
</table>

Abbreviations:
R-MCI: Revised-Myeloma Comorbidity Index; VCD: Bortezomib, Cyclophosphamide, Dexamethasone; IMiD: Immunomodulatory drug; RAD: Lenalidomide, Adriamycin, Dexamethasone; VRd: Bortezomib, Lenalidomide, Dexamethasone; SAE: Serious Adverse Event; SCT: Stem Cell Transplant; CR: Complete Remission; vgPR: very good Partial Remission; PR: Partial Remission; SD: Stable Disease; PD: Progressive Disease

¹ Lead agent prioritization was based on expected severity of AEs; lead agents were rated: alkylating agents first, subsequently IMiDs and PI/Ab, and last anthracyclines or glucocorticoids; i.e. in VCD: Cyclophosphamide was the lead agent

² Others: Proteasome inhibitors, antibodies, anthracyclines, glucocorticoids
Figure legends

**Figure 1. Serious Adverse Events in R-MCI subgroups**
(A) Hematological SAEs CTC 3-4: Distribution in entire cohort and R-MCI subgroups in percentage. Leukocytopenia: p=0.0008; thrombocytopenia: p=0.0007; anemia= <0.0001.
(B) Non-hematological SAEs CTC Grades 3-5 in R-MCI subgroups per patient.
Abbreviations: SAE: Serious Adverse Event; CTC: Common Toxicity Criteria; R-MCI: Revised-Myeloma Comorbidity Index; pt.: patient

**Figure 2. Kaplan-Meier plots for entire cohort and different risk group distributions**
(A) OS and (B) PFS in entire Cohort.
(C) OS and (D) PFS in R-MCI subgroups.
(E) OS and (F) PFS in R-MCI subgroups fit & intermediate vs. frail.
(G) OS and (H) PFS in age groups.
Abbreviations: R-MCI: Revised-Myeloma Comorbidity Index; Int: Intermediate-fit

**Figure 3. Kaplan-Meier plots for patients without or with Serious Adverse Events and patients without or with initial Dose Reduction**
(A) OS and (B) PFS in patients without or with any SAE.
(C) OS and (D) PFS in patients without or with any hematological SAE.
(E) OS and (F) PFS in patients without or with any non-hematological SAE.
(G) OS and (H) PFS in patients without or with DR.
Abbreviations: R-MCI: Revised-Myeloma Comorbidity Index; SAE: Serious Adverse Event; DR: Dose reduction

**Figure 4. Changes in R-MCI scoring from start of induction (T0) to 6-24 months after first R-MCI assessment (T1) in 180 follow-up patients**
Abbreviations: R-MCI: Revised-Myeloma Comorbidity Index; Interm.-fit= Intermediate-fit
Figure 1
Figure 2

Overall Survival

A

Progression Free Survival

B

C

D

E

F

G

H

P-values:

- C: p=0.0688
- D: p<0.0001
- E: p=0.0245
- F: p<0.0001
- G: p=0.1362
- H: p=0.0569
Figure 3

Overall Survival

- **A**: Overall Survival for SAE (no and yes)
  - Patients at risk (n): no SAE 129, 101, 47; SAE 107, 76, 22
  - Years from start of induction: 0, 3, 6, 9, 12, 15, 18, 21
  - p-value: 0.0086

- **C**: Overall Survival for SAE haematological (no and yes)
  - Patients at risk (n): no SAE 147, 113, 52; SAE 89, 64, 17
  - Years from start of induction: 0, 3, 6, 9, 12, 15, 18, 21
  - p-value: 0.0280

- **E**: Overall Survival for SAE non-haematological (no and yes)
  - Patients at risk (n): no SAE 177, 137, 60; SAE 59, 40, 9
  - Years from start of induction: 0, 3, 6, 9, 12, 15, 18, 21
  - p-value: 0.0054

Progression Free Survival

- **B**: Progression Free Survival for SAE (no and yes)
  - Patients at risk (n): no SAE 129, 70, 21; SAE 107, 43, 10
  - Years from start of induction: 0, 3, 6, 9, 12, 15, 18, 21
  - p-value: 0.0527

- **D**: Progression Free Survival for SAE haematological (no and yes)
  - Patients at risk (n): no SAE 147, 77, 23; SAE 89, 36, 8
  - Years from start of induction: 0, 3, 6, 9, 12, 15, 18, 21
  - p-value: 0.0482

- **F**: Progression Free Survival for SAE non-haematological (no and yes)
  - Patients at risk (n): no SAE 177, 95, 29; SAE 59, 18, 2
  - Years from start of induction: 0, 3, 6, 9, 12, 15, 18, 21
  - p-value: 0.0021

Initial dose reduction

- **G**: Initial dose reduction (no and yes)
  - Patients at risk (n): no SAE 148, 119; SAE 102, 58
  - Years from start of induction: 0, 3, 6, 9, 12, 15, 18, 21
  - p-value: <0.0711

- **H**: Initial dose reduction (no and yes)
  - Patients at risk (n): no SAE 148, 78; SAE 102, 35
  - Years from start of induction: 0, 3, 6, 9, 12, 15, 18, 21
  - p-value: <0.0358
**Follow-up:**

Improved/stable = 90%

Deteriorated = 10%

**Follow-up:**

43%

47%

10%

∑: R-MCI changes T0 → T1

**Baseline**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Median R-MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit: 61</td>
<td>3</td>
</tr>
<tr>
<td>Interm.-fit: 107</td>
<td>5</td>
</tr>
<tr>
<td>Frail: 12</td>
<td>8</td>
</tr>
</tbody>
</table>

**Follow-up**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Median R-MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit: 83</td>
<td>2</td>
</tr>
<tr>
<td>Interm.-fit: 85</td>
<td>4</td>
</tr>
<tr>
<td>Frail: 12</td>
<td>7</td>
</tr>
</tbody>
</table>
### Supplementary Table 1A. Hematological SAEs in pts with no (Ø) / with DR & impact on subsequent therapy continuation

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort</th>
<th>Fit</th>
<th>Intermediate</th>
<th>Frail</th>
<th>&lt;60 years</th>
<th>60-69 years</th>
<th>≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts Ø DR : with DR (%)</td>
<td>148 (59) : 102 (41)</td>
<td>59 (81) : 14 (19)</td>
<td>80 (55) : 65 (45)</td>
<td>9 (28) : 23 (72)</td>
<td>80 (79) : 21 (21)</td>
<td>43 (57) : 33 (43)</td>
<td>25 (34) : 48 (66)</td>
</tr>
<tr>
<td>SAEs in pts with Ø DR : with DR (per pt)</td>
<td>92 (0.6) : 65 (0.6)</td>
<td>15 (0.3) : 2 (0.1)</td>
<td>66 (0.8) : 39 (0.6)</td>
<td>11 (1.2) : 24 (1.0)</td>
<td>46 (0.6) : 8 (0.4)</td>
<td>23 (0.5) : 21 (0.6)</td>
<td>23 (0.9) : 36 (0.8)</td>
</tr>
<tr>
<td>Therapy adaptations* in pts after SAEs with Ø DR : with DR (%)</td>
<td>5 (5) : 8 (12)</td>
<td>0 (0) : 0 (0)</td>
<td>2 (3) : 5 (13)</td>
<td>3 (27) : 3 (13)</td>
<td>0 (0) : 1 (13)</td>
<td>2 (9) : 2 (10)</td>
<td>3 (13) : 5 (14)</td>
</tr>
</tbody>
</table>

### Supplementary Table 1B. Non-hematological SAEs in pts with no (Ø) / with DR & impact on subsequent therapy continuation

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort</th>
<th>Fit</th>
<th>Intermediate</th>
<th>Frail</th>
<th>&lt;60 years</th>
<th>60-69 years</th>
<th>≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts Ø DR : with DR (%)</td>
<td>148 (59) : 102 (41)</td>
<td>59 (81) : 14 (19)</td>
<td>80 (55) : 65 (45)</td>
<td>9 (28) : 23 (72)</td>
<td>80 (79) : 21 (21)</td>
<td>43 (57) : 33 (43)</td>
<td>25 (34) : 48 (66)</td>
</tr>
<tr>
<td>SAEs in pts with Ø DR : with DR (per pt)</td>
<td>53 (0.4) : 70 (0.7)</td>
<td>15 (0.3) : 2 (0.1)</td>
<td>33 (0.4) : 37 (0.6)</td>
<td>5 (0.6) : 31 (1.4)</td>
<td>29 (0.4) : 5 (0.2)</td>
<td>15 (0.4) : 29 (0.9)</td>
<td>9 (0.4) : 36 (0.8)</td>
</tr>
<tr>
<td>Therapy adaptations* in pts after SAEs with Ø DR : with DR (%)</td>
<td>14 (26) : 14 (20)</td>
<td>3 (20) : 0 (0)</td>
<td>8 (24) : 6 (16)</td>
<td>3 (60) : 8 (26)</td>
<td>5 (17) : 0 (0)</td>
<td>5 (33) : 4 (14)</td>
<td>4 (44) : 10 (28)</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- DR: Dose Reduction; SAE: Serious Adverse Event; pt.: patient; Ø: No;
- *Adaptations: DR, therapy pause or -discontinuation
<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>R-MCI score</th>
<th>Initial DR: Yes/No</th>
<th>Reason for therapy discontinuation</th>
<th>Therapy cycle of discontinuation</th>
<th>Possible avoidance of therapy discontinuation and/or SAE diminution with better tailored therapy?</th>
<th>R-MCI helpful in tailored therapy decisions: Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>3 = fit</td>
<td>Yes</td>
<td>Persisting neutropenia</td>
<td>4\textsuperscript{th} VCD cycle</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>3 = fit</td>
<td>No</td>
<td>Acute heart and renal failure (MM with concomitant AL-amyloidosis); unsuccessful in-hospital resuscitation</td>
<td>3\textsuperscript{rd} VCD cycle</td>
<td>Yes</td>
<td>Yes*\textsuperscript{1}</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>5 = interm.</td>
<td>Yes</td>
<td>Acute respiratory insufficiency with opiate overdose; reduced general condition</td>
<td>1\textsuperscript{st} VCD cycle</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>7 = frail</td>
<td>Yes</td>
<td>Reduced general condition; multifactorial-induced reduced vigilance</td>
<td>1\textsuperscript{st} VCD cycle</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>77</td>
<td>7 = frail</td>
<td>Yes</td>
<td>Sepsis</td>
<td>4\textsuperscript{th} VCD cycle</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>84</td>
<td>7 = frail</td>
<td>Yes</td>
<td>Acute heart failure; infection</td>
<td>4\textsuperscript{th} RD cycle</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>77</td>
<td>8 = frail</td>
<td>Yes</td>
<td>Acute renal failure; MM progression</td>
<td>3\textsuperscript{rd} VCD cycle</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>8 = frail</td>
<td>Yes</td>
<td>Reduced vigilance; metabolic acidosis; transfer to intensive care unit</td>
<td>1\textsuperscript{st} VCD cycle</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Median (range):**
- Median Age: 72 (58-84) years
- Median R-MCI score: 7 (3-8)
- Median Number of complications: 7/8 = most with DR
- Median Number of therapy-induced complications: 3 (1-4)

<table>
<thead>
<tr>
<th>Possible avoidance of therapy discontinuation and/or SAE diminution with better tailored therapy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 7/8 = most induction protocols were overdosed, suggesting this rather than underdosining the larger clinical challenge*\textsuperscript{2}</td>
</tr>
</tbody>
</table>

**R-MCI helpful in tailored therapy decisions:**
- Yes: Yes
- No: No

**Abbreviations:**
- MM: Multiple myeloma
- R-MCI: Revised-Myeloma Comorbidity Index
- interm.: intermediate-fit
- DR: Dose Reduction
- SAE: Serious Adverse Event
- pt: patient
- VCD: Bortezomib, Cyclophosphamide, Dexamethasone
- Rd: Lenalidomide, Dexamethasone

*\textsuperscript{1} R-MCI-score results in AL-amyloidosis vs. MM patients have proven to be similar, albeit amyloidosis patient constitution was generally more impaired, suggesting that via R-MCI-fitter deemed amyloidosis patients must be regarded much sicker and treated with utmost care as compared to MM patients; see details in Schoeller K, Ihorst G, Engelhardt M et al. Blood 2019; 134 (Supplement_1): 3474. doi: https://doi.org/10.1182/blood-2019-127030

## Supplementary Table 3. Number of patients who suffered ≥1 SAE CTC 3-5 divided in R-MCI groups

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort</th>
<th>Fit</th>
<th>Intermediate</th>
<th>Frail</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>250</td>
<td>73</td>
<td>145</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>≥1 hematological and/or non-hematological SAE (%)</td>
<td>120 (48)</td>
<td>18 (25)</td>
<td>80 (55)</td>
<td>22 (69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥1 hematological SAE (%)</td>
<td>101 (40)</td>
<td>14 (19)</td>
<td>67 (46)</td>
<td>20 (63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anemia (%)</td>
<td>76 (30)</td>
<td>9 (12)</td>
<td>50 (34)</td>
<td>17 (53)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leukocytopenia (%)</td>
<td>56 (22)</td>
<td>5 (7)</td>
<td>42 (29)</td>
<td>9 (28)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Thrombocytopenia (%)</td>
<td>25 (10)</td>
<td>3 (4)</td>
<td>13 (9)</td>
<td>9 (28)</td>
<td>0.0007</td>
</tr>
<tr>
<td>≥1 non-hematological SAE (%)</td>
<td>67 (27)</td>
<td>8 (11)</td>
<td>41 (28)</td>
<td>18 (56)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥1 infectious SAE (%)</td>
<td>56 (22)</td>
<td>8 (11)</td>
<td>35 (24)</td>
<td>13 (41)</td>
<td>0.0006</td>
</tr>
<tr>
<td>≥1 renal SAE (%)</td>
<td>19 (8)</td>
<td>2 (3)</td>
<td>10 (7)</td>
<td>7 (22)</td>
<td>0.0020</td>
</tr>
<tr>
<td>≥1 pulmonary SAE (%)</td>
<td>15 (6)</td>
<td>2 (3)</td>
<td>9 (6)</td>
<td>4 (13)</td>
<td>0.0587</td>
</tr>
<tr>
<td>≥1 cardiac SAE (%)</td>
<td>12 (5)</td>
<td>2 (3)</td>
<td>5 (3)</td>
<td>5 (16)</td>
<td>0.0193</td>
</tr>
<tr>
<td>Leukocytopenia &amp; ≥1 infectious SAE (%)</td>
<td>25 (10)</td>
<td>1 (1)</td>
<td>18 (12)</td>
<td>6 (19)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- R-MCI: Revised-Myeloma Comorbidity Index
- SAE: Serious Adverse Event

## Supplementary Table 4. First response after start of induction in R-MCI subgroups

<table>
<thead>
<tr>
<th>R-MCI subgroups</th>
<th>CR</th>
<th>vgPR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit pts (%)</td>
<td>1 (1%)</td>
<td>19 (26%)</td>
<td>33 (45%)</td>
<td>16 (22%)</td>
<td>4 (6%)</td>
<td>73</td>
</tr>
<tr>
<td>Intermediate-fit pts (%)</td>
<td>1 (1%)</td>
<td>32 (22%)</td>
<td>79 (54%)</td>
<td>26 (18%)</td>
<td>7 (5%)</td>
<td>145</td>
</tr>
<tr>
<td>Frail pts (%)</td>
<td>1 (3%)</td>
<td>8 (25%)</td>
<td>13 (40.5%)</td>
<td>6 (19%)</td>
<td>4 (12.5%)</td>
<td>32</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- R-MCI: Revised-Myeloma Comorbidity Index
- CR: Complete Remission
- vgPR: very good Partial Remission
- PR: Partial Remission
- SD: Stable Disease
- PD: Progressive Disease
- Sum: summary
Supplementary figure legends

**Supplementary Figure 1. R-MCI with via multivariate analysis generated prognostic factors**
Abbreviations: R-MCI: Revised-Myeloma Comorbidity Index; FEV1: Forced expiratory volume in 1 second; KPS: Karnofsky Performance Status, TUG: Timed Up and Go; IADL: Instrumental Activities of Daily Living; eGFR: estimated Glomerular Filtration Rate;
1 Lung dysfunction: Mild: FEV1 <80%; moderate: FEV1 ≤60% or diffusion capacity ≤61%, severe: FEV1 <50%; mild: 0/1 parameter is correct; moderate: 2 parameters are correct; severe: >2 parameters are correct
2 Frailty: Karnofsky Index ≤70%; Time Up/Go >10 seconds; IADL ≤4 points; subjective fitness grade E or F
3 Unfavorable: del17p13, t(4;14), t(14;16), t(14;20), chromosome 1 abnormalities, c-myc, del(13q14), hypodiploidy

**Supplementary Figure 2. Consort flow diagram: study design**
Abbreviations: MM: Multiple Myeloma; SAE: Serious Adverse Event; OS: Overall Survival; PFS: Progression Free Survival; R-MCI: Revised-Myeloma Comorbidity Index; y: years

**Supplementary Figure 3. VCD vs. non-VCD distribution in entire cohort and in follow-up cohort with R-MCI changes from start of induction (T0) to 6-24 months after first R-MCI assessment (T1)**
Abbreviations: VCD: Bortezomib, Cyclophosphamide, Dexamethasone; RAD: Lenalidomide, Adriamycin, Dexamethasone; VRd: Bortezomib, Lenalidomide, Dexamethasone; RD: Lenalidomide, Dexamethasone; IdaD: Idarubicin, Dexamethasone
*Others: Vd: Bortezomib, Dexamethasone; RCD: Lenalidomide, Cyclophosphamide, Dexamethasone; CD: Cyclophosphamide, Dexamethasone; TD: Thalidomide, Dexamethasone; MVP: Melphanal, Bortezomib, Prednisolone; VTD: Bortezomib, Thalidomide, Dexamethasone; Elo-VRd: Elotuzumab, Bortezomib, Lenalidomide, Dexamethasone
**R-MCI (0-9 points)**

- **Lungdysfunction**\(^1\):
  - (FEV 1/diffusion capacity)
  - No/mild: 0
  - Moderate/severe: 1

- **Renal function**:
  - (eGFR ml/min/1.73m\(^2\))
  - \(\geq 60\): 0
  - <60: 1

- **Karnofsky Performance Status**:
  - 100%: 0
  - 80 or 90%: 2
  - \(\leq 70\%\): 3

- **Cytogenetics**:
  - Favorable: 0
  - Unfavorable\(^3\): 1
  - Missing: 0

- **Frailty**\(^2\):
  - (KPS, TUG, IADL, subjective fitness)
  - No/mild: 0
  - Moderate/severe: 1

- **Age**:
  - In years
  - <60: 0
  - 60-69: 1
  - \(\geq 70\): 2

**Supplementary Figure 1**
Induction therapy survey of 359 patients
(Prospective geriatric assessments university Freiburg & inclusion in MM-tumorboard)

250 patients (100%) for detailed analysis

Assessment of induction protocols, SAE, adaptations, response, OS / PFS

R-MCI subgroups: fit / intermediate-fit / frail

Age groups: < 60y / 60-69y / ≥ 70y

Exclusion of 70 patients (28%: insufficient data for R-MCI follow-up)

180 patients (72%) with follow-up after 6-24 months

Supplementary Figure 2
### Entire cohort (250 patients)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>VCD</th>
<th>RAD/VRd/RD</th>
<th>IdaD/Others*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>176</td>
<td>18 17 9</td>
<td>5 25</td>
</tr>
</tbody>
</table>

### Follow-up cohort (180 patients)

<table>
<thead>
<tr>
<th>Treatment induction: VCD vs. non-VCD</th>
<th>Median / mean (range) R-MCI T0</th>
<th>Median / mean (range) R-MCI T1</th>
<th>Mean difference R-MCI T0→T1 (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCD (n=127)</td>
<td>5 / 4.6 (0-9)</td>
<td>4 / 3.9 (0-8)</td>
<td>-0.7 (4↓ - 3↑)</td>
</tr>
<tr>
<td>Non-VCD (n=53)</td>
<td>3 / 3.5 (0-7)</td>
<td>3 / 3.2 (0-7)</td>
<td>-0.3 (2↓ - 3↑)</td>
</tr>
</tbody>
</table>

| p-value                              | <0.0001                         | <0.0051                         | <0.0535                          |

**Supplementary Figure 3**