First-line therapy with either bortezomib-melphalan-prednisone or lenalidomide-dexamethasone followed by lenalidomide for transplant-ineligible multiple myeloma patients: a pooled analysis of two randomized trials

by Alessandra Larocca, Roberto Mina, Massimo Offidani, Anna Marina Liberati, Antonio Ledda, Francesca Patriarca, Andrea Evangelista, Stefano Spada, Giulia Benevolo, Daniela Oddolo, Vanessa Innao, Clotilde Cangialosi, Annalisa Bernardini, Pellegrino Musto, Valeria Amico, Vincenzo Fraticelli, Laura Paris, Nicola Giuliani, Antonietta Pia Falcone, Renato Zambello, Lorenzo De Paoli, Alessandra Romano, Antonio Palumbo, Vittorio Montefusco, Roman Hajek, Mario Boccadoro, and Sara Bringhen

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First-line therapy with either bortezomib-melphalan-prednisone or lenalidomide-dexamethasone followed by lenalidomide for transplant-ineligible multiple myeloma patients: a pooled analysis of two randomized trials

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**Running title**: First-line therapy in elderly myeloma patients

**Keywords**: Multiple myeloma, newly diagnosed, elderly, bortezomib, lenalidomide
Abstract

Bortezomib-melphalan-prednisone and continuous lenalidomide-dexamethasone represent the standard treatment of transplant-ineligible, newly diagnosed multiple myeloma patients. To date, no randomized trial has compared bortezomib-melphalan-prednisone to lenalidomide-dexamethasone, and there is no evidence of the optimal treatment for newly diagnosed multiple myeloma, particularly in high-risk cytogenetic patients (del(17p), t(4;14) or t(14;16)). We pooled together data from newly diagnosed myeloma patients treated with bortezomib-melphalan-prednisone or lenalidomide-dexamethasone induction followed by lenalidomide maintenance 10 mg enrolled in the GIMEMA-MM-03-05 and EMN01 trials, to evaluate their efficacy in different patient subgroups, focusing on standard and high-risk cytogenetics. Overall, 474 patients were analyzed (bortezomib-melphalan-prednisone: 257 patients; lenalidomide-dexamethasone followed by lenalidomide maintenance: 217 patients). No difference in progression-free survival (Hazard Ratio: 0.96) and overall survival (Hazard Ratio: 1.08) was observed between bortezomib-melphalan-prednisone and lenalidomide-dexamethasone followed by lenalidomide in standard-risk, while a reduction in the risk of progression (Hazard Ratio: 0.54) and death (Hazard Ratio: 0.73) was seen in high-risk patients treated with bortezomib-melphalan-prednisone vs. lenalidomide-dexamethasone followed by lenalidomide. In particular, standard risk patients >75 years benefited less from bortezomib-melphalan-prednisone than lenalidomide-dexamethasone followed by lenalidomide (Hazard Ratio for progression-free survival: 0.96; Hazard Ratio for overall survival: 1.81).

In this non-randomized analysis, bortezomib-melphalan-prednisone and lenalidomide-dexamethasone followed by lenalidomide were equally effective in younger (≤75 years), standard-risk patients, while older ones (>75 years) benefited more from lenalidomide-
dexamethasone followed by lenalidomide. In high-risk patients, bortezomib-melphalan-prednisone improved progression-free survival and overall survival irrespective of age. The source trials are registered at ClinicalTrials.gov (NCT01063179 and NCT01093196).
Introduction

Multiple myeloma (MM) is mainly a disease of the elderly, being the median age at diagnosis 71 years and 2/3 of patients older than 65 years of age. Elderly patients, defined as older than 65-70 years of age, are usually considered ineligible for high-dose chemotherapy and autologous stem-cell transplant. In Europe, standard initial therapy of older patients consists of either a triplet regimen including bortezomib-melphalan-prednisone (VMP) administered in a fixed-duration schedule, or a doublet combination of lenalidomide (25 mg) and dexamethasone (Rd), administered continuously until progression or intolerance. The VISTA trial demonstrated that VMP was superior to melphalan-prednisone (MP) both in terms of progression-free survival (PFS, 21.7 vs. 15.2 months, HR, 0.56, P<0.001) and overall survival (OS, 56.4 vs 43.1 months, HR 0.69; P<0.001). The FIRST trial showed that continuous Rd significantly prolonged median PFS (26 vs 21.9 months; HR 0.69, P< 0.001) and OS (59.1 vs 49.1 months; HR, 0.78, P=0.0023) versus the melphalan-prednisone-thalidomide (MPT). Based on the results of these two phase III studies, both VMP and continuous Rd were approved by the European Medicine Agency as standard treatments for patients with newly diagnosed MM (NDMM) ineligible for autologous stem-cell transplantation (ASCT).

The most important prognostic factors in MM are age and frailty, disease stage defined by the international staging system (ISS), and chromosomal abnormalities, detected by fluorescent in situ hybridization (FISH). Patients harboring chromosomal abnormalities including del(17p), t(4,14) and t(14,16) have a poor prognosis, with a higher risk of disease progression and death. Approximately 15-20% of NDMM patients present with at least one cytogenetic abnormality and represent the so called “high-risk” population. Despite recent therapeutic advances in MM, the results obtained with novel agent-based regimens in patients with high-risk chromosomal abnormalities are unsatisfactory and their prognosis remains poor. Moreover, limited data are available on high-risk, transplant-
ineligible MM patients treated with bortezomib or lenalidomide in first-line therapy. In the VISTA trial, high vs standard-cytogenetic risk patients receiving VMP had similar time to progression (median 19.8 vs 23.1 months; HR: 1.29, p=0.55) and OS (HR: 1.00, p=0.99). In a sub-analysis of the FIRST trial, continuous Rd treatment resulted in PFS and OS benefits vs MPT; however, these differences were largely due to the PFS and OS improvements in patients without high-risk cytogenetics (median PFS 31.1 vs 21.2 vs 24.9 months for continuous Rd vs Rd18 vs MPT). Indeed, in the high-risk group, the longest PFS was observed with Rd18 treatment (median 8.4 vs 17.5 vs 14.6 months for continuous Rd vs Rd18 vs MPT) while OS was similar across treatment arms.

Unfortunately, VMP and Rd have never been formally compared in a randomized trial. Based on the different safety profiles of bortezomib and lenalidomide, in patients with advanced renal failure the use of bortezomib is usually preferred, while in patients with pre-existing neuropathy, or when oral therapy is preferable, lenalidomide can be the drug of choice.

Besides these considerations, VMP and Rd are equally recommended. Because a head-to-head comparison between VMP vs Rd is lacking, the choice of first-line treatment of elderly MM patients is mainly based on physician's and patient's preference.

We previously published the results of two randomized, phase III, studies investigating both VMP (GIMEMA-MM-03-05) and Rd induction followed by lenalidomide maintenance (Rd-R) (EMN01) as upfront therapies for elderly, transplant-ineligible MM patients. In order to provide clinicians with useful, and currently lacking evidence, that may help to better tailor anti-myeloma treatment in this population, we conducted a pooled, retrospective analysis comparing the efficacy of VMP and Rd-R in different subgroups of elderly, transplant-ineligible MM patients, focusing on cytogenetic profile.

Methods
Study design and participants

We pooled together single data from two phase III studies, the GIMEMA-MM-03-05 (NCT01063179) and the EMN01 (NCT01093196) trials. Both trials enrolled NDMM patients older than 65 years of age or younger but ineligible for ASCT. Inclusion and exclusion criteria, as well as treatment details of the source studies, were previously published (Supplementary Appendix). Further details on study treatments and procedures are reported in Supplementary Appendix. For this retrospective, not pre-planned analysis, we selected only patients randomized to VMP and Rd followed by lenalidomide maintenance (Rd-R). The source studies were approved by the institutional review boards at each of the participating centers. All patients gave written informed consent before entering the source studies, which were performed in accordance with the Declaration of Helsinki.

Statistical analysis

The primary objective of this analysis was to compare PFS and OS (see Supplementary Appendix) in patients treated with VMP and Rd-R adjusting for patient and disease characteristics at baseline.

Single data from the two studies were pooled together and analyzed. Comparisons between different patient groups were investigated using standard statistical tests. Time-to-event data were analyzed using the Kaplan–Meier method; survival curves were compared with the log-rank test. Results are presented as hazard ratios (HRs), 95% confidence intervals (95% CIs), and two-sided p-values adjusted for age, ISS stage, cytogenetic risk by FISH, Karnofsky performance status (PS) and extramedullary disease (yes vs no) [main model]. Subgroup analyses were performed to determine the consistency of treatment effects of VMP vs Rd-R in the main model in the different subgroups using interaction terms between treatment and cytogenetic (also with single deletion and translocation, del(17p), t(4;14) and t(14;16)), ISS
stage (I vs II/III), age (≤75 vs >75 years), Karnofsky PS (90-100 vs 70-80 vs 60) and extramedullary disease. The null hypothesis that is tested with the interaction test is that the HR of the comparison VMP vs Rd-R is the same in each subgroup. The models were adjusted for age as continuous variable. Multivariate Cox models with three-way interaction between treatment (VMP vs Rd-R), cytogenetic (high-risk vs standard-risk, missing vs standard-risk) and age (≤75 vs >75 years) were performed to evaluate the effect of treatment in different cytogenetic and age subgroups. The models were adjusted for other factors included in previous analysis. The different effect of VMP vs Rd-R in cytogenetic subgroups was confirmed by a sensitivity analysis using the multiple imputation method for missing cytogenetic and ISS values. In particular, missing data were handled using “jomo” package\textsuperscript{16} to perform Cox model compatible multiple imputation\textsuperscript{17,18} with 50 imputations, 1,000 burn-in iterations and 1,000 iterations between two successive imputations.

In both trials, FISH was centrally assessed with a 10% cut-off for numerical aberrations and a 15% one for IgH translocations. High-risk cytogenetics was defined as presence of at least one of the following chromosomal abnormalities: del(17p), or t(4;14) or t(14;16). Patients not carrying any of these abnormalities were defined as standard-risk patients. Data were censored on 18\textsuperscript{th} June, 2014 for the GIMEMA-MM-03-05 study and on 20\textsuperscript{th} October, 2017 for the EMN01 study. Data were analyzed using R software (Version 3.5.1).

Results
Patients

A total of 474 patients were analyzed, 257 in the VMP group and 217 in the Rd-R group. Patients’ demographic and baseline characteristics were rather balanced between the two groups (Table 1). Median age of the overall population was 72 years (IQR 69-76), with patients in Rd-R group being slightly older (median, 73 years; IQR 70-77) than patients in the
VMP group (median, 71 years; IQR 68-75; p<0.001). A similar proportion of patients in the VMP and Rd-R groups had ISS III (23% vs 27%; p=0.74) and high-risk cytogenetics by FISH (19% vs 22%; p=1).

All patients started the assigned treatment. Overall, 61% and 64% of patients in the VMP and Rd-R groups, respectively, received a second-line treatment, which consisted of an immunomodulatory drug (IMiD)-based regimen in 63% of patients treated with VMP and of a proteasome inhibitor (PI)-based regimen in 84% of patients treated with Rd-R (table 2).

Median follow-up for the entire study population was 70.2 months (IQR 54.7 - 80.6), without significant differences between VMP (72.6 months) and Rd-R (64.4 months; p=0.16).

**Survival outcomes**

In the overall population, median PFS was 21.5 months (95% CI 19.8-24.9), without significant differences between VMP (25.1 months, 95% CI 20.9-28.6) and Rd-R patients (18.6 months, 95% CI 16-22.4; HR:0.81, p=0.07), with 15% and 18% of patients alive and free from progression at 5 years, in the VMP and Rd-R groups, respectively. In the subgroup analysis (Figure 1), no clear differences in PFS between VMP and Rd-R were noticed according to age (in patients ≤75 years, HR: 0.80; in patients >75 years, HR: 0.84, interaction p= 0.85), Karnofsky PS (score 90-100, HR: 0.73; score 70-80, HR: 0.86, interaction p= 0.43), ISS (stage I, HR: 0.73; stage II/III, HR: 0.85, interaction p= 0.55) and the presence of extramedullary disease (yes, HR: 0.75; no, HR: 0.82, interaction p= 0.78). Among standard-risk patients by FISH, no difference in PFS was observed between VMP and Rd-R groups (HR: 0.96, 95% CI 0.73-1.28); while, in high-risk patients, a significant benefit was observed with VMP in comparison with Rd-R (HR: 0.54, 95% CI 0.34-0.84; interaction-p=0.03). The advantage of VMP over Rd-R in high-risk patients was confirmed in the single high-risk cytogenetic
abnormalities subgroups, including del(17p) (HR: 0.59, 95% CI 0.32-1.09), t(4;14) (HR: 0.50, 95% CI 0.27-0.93) and t(14;16) (HR: 0.35, 95% CI 0.09-1.42) (Figure S1).

Median OS in the overall population was 66.4 months (95% CI 57.3-79.7); median OS was not significantly different between VMP (71 months; 95% CI 58.2-NR) and Rd-R patients (62 months, 95% CI 48.2-83.3; HR: 0.85, p=0.28), with an equivalent proportion of patients alive at 5 years (55% vs 51%, respectively). In the subgroup analysis (Figure 2), patients ≤75 years benefited more from VMP than Rd-R (HR: 0.71, 95% CI 0.51-1.00), whereas patients >75 years benefited more from Rd-R (HR: 1.29, 95% CI 0.79-2.13; interaction-p=0.04). Similarly to PFS, no significant difference in OS was noted in standard-risk patients between VMP and Rd-R (HR: 1.08, 95% CI 0.74-1.58), but a OS advantage for VMP over Rd-R was reported in high-risk ones (HR: 0.73, 0.42-1.26) and in those with missing data. The advantage for VMP over Rd-R in high-risk patients was confirmed in the single high-risk cytogenetic abnormalities subgroups, including del(17p) (HR: 0.81, 95% CI 0.38-1.71), t(4;14) (HR: 0.74, 95% CI 0.35-1.56), and t(14;16) (HR: 0.73, 95% CI 0.13-4.05) (Figure S2).

Multivariate Cox models with three-way interaction were performed to better evaluate the relationship between treatment regimen (VMP vs Rd-R), age (≤75 vs >75 years) and cytogenetic risk (standard vs high). This analysis confirmed the absence of PFS difference between VMP and Rd-R according to age in the standard-risk group, while confirmed the PFS benefit with VMP over Rd-R in high-risk patients (interaction-p=0.03). In terms of OS, older (>75 years), standard-risk patients seemed to benefit more from Rd-R than VMP (HR: 1.81), while the OS advantage with VMP was confirmed in younger (≤75 years), standard-risk patients (HR: 0.83). In high-risk patients, the OS benefit was confirmed irrespective of age (≤75 years, HR: 0.75; >75 years, HR: 0.65) (Table 3).

To better investigate the comparison between VMP vs Rd-R and the effect of cytogenetics and age we performed a multiple imputation analysis for cytogenetics and ISS stage missing
No difference in PFS was observed between VMP and Rd-R (HR: 0.85, 95% CI 0.69-1.04); subgroup analysis confirmed the previous results for cytogenetics, with no difference for standard-risk patients (HR: 1.01, 95% CI 0.78-1.30); while, in high-risk patients, a significant benefit was observed with VMP in comparison with Rd-R (HR: 0.53, 95% CI 0.34-0.82; interaction-p=0.02) (Figure S3). No difference in OS was observed between VMP and Rd-R (HR: 0.86, 95% CI 0.66-1.13); subgroup analysis confirmed benefits of VMP for patients ≤75 years than Rd-R (HR: 0.72, 95% CI 0.52-0.99), whereas patients >75 years benefited more from Rd-R (HR: 1.29, 95% CI 0.79-2.08; interaction-p=0.05) (Figure S4).

Multivariate Cox models with three-way interaction confirm the result for PFS and OS (Table S1).

Discussion

In this pooled analysis of 474 transplant-ineligible patients with NDMM, we evaluated the impact on survival outcomes of initial treatment, consisting of either a bortezomib-based regimen (VMP) or a lenalidomide-based one (Rd-R), in different subgroups of patients, focusing on cytogenetic risk profile by FISH. We found no difference between VMP and Rd-R in standard-risk patients, whereas, in high-risk patients, VMP improved PFS (HR: 0.54) and OS (HR: 0.73) as compared to Rd-R.

Risk assessment and stratification have long been performed in MM, taking into consideration both the aggressiveness of the disease at presentation, based on ISS stage, and its cytogenetic features, either by FISH or gene expression profile. Many prognostic factors have been identified in myeloma, the most important ones being chronological and biological age, defined by frailty status in elderly patients, and the presence of chromosomal abnormalities by FISH.11
Although the risk assessment had limited impact on therapeutic choices in the past, with the expanding treatment armamentarium of MM and the growing evidence of effect modification, it is likely to become a fundamental factor to select and tailor treatment. The IMWG guidelines recommend that all NDMM patients be screened for chromosomal abnormalities by FISH, including del(17p), t(4;14) and t(14;16), and that all older patients undergo a geriatric assessment for the evaluation of frailty. Despite these recommendations, to date no trial has prospectively evaluated the efficacy of standard therapies according to patients’ risk status, either based on chromosomal abnormalities by FISH or on frailty status. Hence, very limited data are available about the efficacy of current standards of care, such as VMP and Rd, for NDMM patients with high-risk cytogenetics. The VISTA trial did not find any difference between high-risk and standard-risk patients treated with VMP. In the FIRST trial, there was no evidence that lenalidomide improved outcome of patients with high-risk cytogenetics. However, the small number of high-risk patients in both trials makes it difficult to draw definitive conclusions.

In our study, we defined high-risk patients as those carrying at least one cytogenetic abnormality, including del(17p), t(4;14) and t(14;16), consistently with the IMWG recommendations. Major advantages of this study are the number of patients with available cytogenetic data and the fact that all FISH analyses were performed at one centralized facility only.

In our analysis, VMP resulted in a 45% reduction in the risk of death or progression as compared to Rd-R (HR: 0.54) in the high-risk group, being the PFS benefit confirmed across the single cytogenetic abnormalities, whereas no significant difference in PFS was found in the standard-risk group (HR: 0.96, interaction-p=0.03). Furthermore, high-risk patients treated with VMP had a reduced risk of death (HR: 0.73), confirmed across all cytogenetic subgroups, in comparison with Rd-R, while no difference between VMP and Rd-R was noticed among
standard-risk ones (HR: 1.08). However, we cannot distinguish the role of melphalan from that of bortezomib in improving the outcome of high-risk patients.

The PFS benefit for VMP over Rd-R in high-risk patients was seen in both younger (≤75 years; HR: 0.75) and older patients (>75 years; HR: 0.19), while in older, standard-risk patients VMP and Rd-R had similar outcome (HR: 0.96). Similarly, while the OS benefit among high-risk patients was independent of age (patients ≤ 75 years, HR: 0.75; patients >75 years, HR: 0.65), older patients with standard-risk cytogenetics benefit less from VMP (patients >75 years, HR: 1.81) than did from Rd-R.

No data about frailty evaluation were available in the GIMEMA-MM-03-05 trial at diagnosis, and chronological age was the only parameter that could be evaluated in both trials. In order to better assess the efficacy of approved upfront regimens according to cytogenetic risk, we restricted our analysis to patients randomized to the VMP arm of the GIMEMA-MM-03-05 trial and the Rd-R arm of the EMN01 trial, since both VMP and Rd are approved combinations for NDMM patients ineligible for transplant. Of note, in the EMN01-trial patients in the Rd-R arm received Rd for 9 cycles followed by lenalidomide maintenance or lenalidomide-prednisone maintenance until progression (lenalidomide 10 mg/day), whereas the standard approved Rd is administered continuously until progression. This could in part explain the inferior PFS in the EMN01 trial (21 months) as compared to the FIRST trial (26 months). On the other hand, we have recently presented at the American Society of Hematology meeting preliminary results of a randomized phase III study comparing standard Rd to Rd-R in older, intermediate fit patients, defined by the IMWG frailty score, showing no difference between continuous Rd and Rd-R in terms of PFS (HR 0.93, 95% CI 0.64-1.34, p=0.681) and OS (HR 0.73, 95% CI 0.40-1.33, p=0.306).

In the VISTA trial bortezomib was given twice weekly during cycles 1 to 4 and twice weekly thereafter, while in the GIMEMA-MM-03-05-trial half of the patients in the VMP arm (n=191,
51%) received once-weekly bortezomib. However, we had previously shown that the once weekly schedule was equally effective to the twice weekly one in a subgroup analysis of the GIMEMA-MM-03-05 study, potentially due to a more tolerable safety profile of once weekly bortezomib. This might explain a somewhat more favorable median PFS with VMP in the GIMEMA-MM-03-05 study (median, 24.8 months) as compared to the PFS (median, 21.7 months) reported in the VISTA trial.

The major limitation of this unplanned cross-trial comparison is the absence of randomization between the 2 treatments, therefore results should be interpreted with more caution. Despite similar eligibility criteria and a comparable follow-up of more than 5 years, there are some significant differences between the two populations. In fact, patients treated with Rd-R were significantly older and patients treated with VMP had a significantly higher creatinine level. Another limitation is that patients enrolled in the two source trials had to meet strict inclusion and exclusion criteria.

Despite these caveats, a head-to-head comparison between VMP vs Rd is currently lacking, as well as a prospective evaluation of different treatments in high-risk and standard-risk MM patients. To the best of our knowledge, this is the first study that pooled together and analyzed a large series of transplant-ineligible, NDMM treated with either a bortezomib or lenalidomide-based combination, with the aim of providing an answer to the burning question of the optimal upfront treatment for NDMM according to their cytogenetic risk.

Our results suggest that the doublet regimen lenalidomide-dexamethasone may be a suboptimal option for patients with high-risk cytogenetics, further supporting the 2016 IMWG recommendations that a triplet regimen containing an IMiD and a PI should be used in this setting. In this light, a major step forward has been made with the results of the SWOG study S0777, that showed superior response rate, PFS and OS with the triplet regimen bortezomib-lenalidomide-dexamethasone (VRD) versus Rd in patients with NDMM without intention to
immediate transplant. Of note, the longest PFS in high-risk patients was obtained with VRD (38 months). Nevertheless, the analysis was based on 44 high-risk patients only.

The selection of treatment in elderly patients should also consider the risk of toxicity and the capability to tolerate treatment, since advanced age and the occurrence of severe adverse events may negatively affect survival. In our analysis, this was particularly evident in standard-risk patients, in whom no difference between VMP and Rd-R was found and the benefit of Rd-R was more evident in patients over 75 years. In this context, the presence of specific comorbidities (such as peripheral neuropathy, renal insufficiency), older age (>75 years) or the presence of frailty, as well as patient’s compliance and preference should be considered when choosing treatment.

Our results highlight the importance of performing FISH analysis in all NDMM for risk stratification. Treatment decision in elderly patients ineligible for transplant is extremely complex, since not only the biology or the disease stage should be considered, but also the characteristics of patients (frailty status, comorbidities, hospitalization, concomitant medications, social support, compliance) and goals of care (depth of response or disease control). Therefore, both VMP or Rd are valid options for transplant-ineligible NDMM patients. Nevertheless, VMP could be preferred in patients with high-risk cytogenetics and severe renal insufficiency, whereas continuous Rd could be the treatment of choice in standard-risk patients, particularly over 75 years, or if oral administration and not inducing peripheral neuropathy are major considerations.

The results of this analysis are based on a selected population, including patients enrolled in clinical trials. Nevertheless, an ongoing trial will prospectively compare these two standard treatments, VMP and continuous Rd, and the impact on outcomes of cytogenetics in an unselected population of patients ≥ 65 years with MM in every day clinical practice (Real MM trial, ClinicalTrials.gov Identifier: NCT03829371).
Better treatment options and newer combinations in high-risk disease are needed. Recent trials incorporating the first in class monoclonal antibody anti-CD38 daratumumab combined with VMP (Dara-VMP)\textsuperscript{23} or Rd (Dara-Rd)\textsuperscript{24} significantly reduced the risk of progression or death by 50\% and 44\%, respectively as compared to standard VMP (Dara-VMP vs VMP: median PFS not reached vs 18.1 months, HR 0.50, 95\% CI, 0.38-0.65) and Rd (Dara_Rd vs Rd: median PFS not reached vs 31.9 months, HR 0.56, 95\% CI 0.43-0.73). The benefit of Dara-VMP and Dara-Rd was evident in most of the subgroups analyzed, however the addition of daratumumab seems not to overcome the poor prognosis of high-risk patients.

Ongoing trials testing multi-drug combinations including immunomodulatory drugs, second-generation PIs, as carfilzomib and ixazomib, or monoclonal antibodies in the frontline setting will evaluate and, potentially, improve the outcome of high-risk patients.
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References.

1. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011;364(11):1046–60.
2. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014. Bethesda, US-MD.
3. Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2017;28(suppl_4):iv52-iv61.
4. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906–917.
5. San Miguel JF, Schlag R, Khuageva NK, et al. Persistent Overall Survival Benefit and No Increased Risk of Second Malignancies With Bortezomib-Melphalan-Prednisone Versus Melphalan-Prednisone in Patients With Previously Untreated Multiple Myeloma. J Clin Oncol. 2013;31(4):448–455.
6. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906–917.
7. Facon T, Dimopoulos MA, Dispenzieri A, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood. 2018;131(3):301–310.
8. Greipp PR, San Miguel J, Durie BGM, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412–3420.
9. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016;127(24):2955–2962.
10. Avet-Loiseau H, Hulin C, Benboubker L, et al. Impact of Cytogenetics on Outcomes of Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma Treated with Continuous Lenalidomide Plus Low-Dose Dexamethasone in the First (MM-020) Trial.
11. Larocca A, Dold SM, Zweegman S, et al. Patient-centered practice in elderly myeloma patients: an overview and consensus from the European Myeloma Network (EMN). Leukemia. 2018;32(8):1697–1712.

12. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: A randomized controlled trial. J Clin Oncol. 2010;28(34):5101–5109.

13. Palumbo A, Bringhen S, Larocca A, et al. Bortezomib-Melphalan-Prednisone-Thalidomide Followed by Maintenance With Bortezomib-Thalidomide Compared With Bortezomib-Melphalan-Prednisone for Initial Treatment of Multiple Myeloma: Updated Follow-Up and Improved Survival. J Clin Oncol. 2014;32(7):634–640.

14. Bringhen S, Larocca A, Rossi D, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood. 2010;116(23):4745–4753.

15. Magarotto V, Bringhen S, Offidani M, et al. Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma. Blood. 2016;127(9):1102–1108.

16. Carpenter JR, Kenward MG. Multiple Imputation and its Application. Chichester, UK: John Wiley & Sons, Ltd. 2015.

17. Bartlett JW, Seaman SR, White IR, Carpenter JR. Multiple imputation of covariates by fully conditional specification: accommodating the substantive model. Stat Methods Med Res. 2015;24(4):462-487.

18. Quartagno M, Carpenter JR. Multilevel Multiple Imputation in presence of interactions, non-linearities and random slopes. 49th Scientific meeting of the Italian Statistical Society.

19. Palumbo A, Bringhen S, Mateos M-V, et al. Geriatric assessment predicts survival and
toxicities in elderly myeloma patients: An International Myeloma Working Group report.
Blood. 2015;125(13):2068–2074.

20. Larocca A, Salvini M, De Paoli L, et al. Efficacy and Feasibility of Dose/Schedule-Adjusted Rd-R Vs. Continuous Rd in Elderly and Intermediate-Fit Newly Diagnosed Multiple Myeloma (NDMM) Patients: RV-MM-PI-0752 Phase III Randomized Study. 2018;132(Suppl 1):305.

21. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017;389(10068):519–527.

22. Bringhen S, Mateos MV, Zweegman S, et al. Age and organ damage correlate with poor survival in myeloma patients: Meta-analysis of 1435 individual patient data from 4 randomized trials. Haematologica. 2013;98(6):980–987.

23. Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med 2018;378(6):518–528.

24. Facon T, Kumar SK, Plesner T, et al. Phase 3 Randomized Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients with Newly Diagnosed Multiple Myeloma (NDMM) Ineligible for Transplant (MAIA). Blood. 2018;132(Suppl 1):LBA-2
Table 1. Baseline patient characteristics in the ITT population.

|                      | All patients (N=474) | VMP (N=257) | Rd-R (N=217) | p-value |
|----------------------|----------------------|-------------|--------------|---------|
| **Age – median (IQR)** |                      |             |              |         |
| >75 years – N (%)    | 131 (28)             | 57 (22)     | 74 (34)      | <0.001  |
| **Karnofsky PS – N (%)** |                      |             |              |         |
| 90-100               | 232 (49)             | 121 (47)    | 111 (51)     | 0.11    |
| 70-80                | 200 (42)             | 118 (46)    | 82 (38)      |         |
| 60                   | 42 (9)               | 18 (7)      | 24 (11)      |         |
| **Creatinine – mg/dL (IQR)** |                  |             |              |         |
|                      | 1 (0.8-1.22)         | 1.01 (0.84-1.3) | 0.94 (0.8-1.19) | 0.002   |
| **LDH – UI/L (IQR)** |                      |             |              |         |
| Missing – N (%)      | 80 (17)              | 36 (14)     | 44 (20)      | 0.753   |
| **Extramedullary**   |                      |             |              |         |
| Disease – N (%)      | 58 (12)              | 37 (14)     | 21 (10)      | 0.124   |
| **ISS – N (%)**      |                      |             |              |         |
| I                    | 117 (25)             | 56 (22)     | 61 (28)      | 0.96    |
| II                   | 184 (39)             | 88 (34)     | 97 (45)      |         |
| III                  | 117 (25)             | 57 (22)     | 59 (27)      |         |
| Missing              | 56 (12)              | 56 (22)     |              |         |
| **Cytogenetics – N (%)** |                    |             |              |         |
| Standard-risk        | 273 (58)             | 136 (53)    | 137 (63)     | 1       |
| High-risk*           | 95 (20)              | 48 (19)     | 47 (22)      |         |
| Missing              | 106 (22)             | 73 (28)     | 33 (15)      |         |
| **Del(17p) – N (%)** |                      |             |              | 1       |
|                  | No          | Yes         | Missing     |
|------------------|-------------|-------------|-------------|
| T(4;14) – N (%)  |             |             |             |
| No               | 321 (68)    | 161 (63)    | 160 (74)    |
| Yes              | 47 (10)     | 23 (9)      | 24 (11)     |
| Missing          | 106 (22)    | 73 (28)     | 33 (15)     |
| **T(4;14) – N (%)** |             |             |             |
| No               | 1.00        |             |             |
| Yes              |             | 0.88        |             |
| Missing          |             |             | 0.88        |
| **T(14;16) – N (%)** |             |             |             |
| No               | 352 (74)    | 178 (69)    | 174 (80)    |
| Yes              | 13 (3)      | 6 (2)       | 7 (3)       |
| Missing          | 109 (23)    | 73 (28)     | 36 (17)     |
| **T(14;16) – N (%)** |             |             |             |
| No               | 1.00        |             |             |
| Yes              |             | 0.785       |             |
| Missing          |             |             | 0.785       |
| **T(11;14) – N (%)** |             |             |             |
| No               | 308 (65)    | 164 (64)    | 144 (66)    |
| Yes              | 54 (11)     | 20 (8)      | 34 (16)     |
| Missing          | 112 (24)    | 73 (28)     | 39 (18)     |
| **T(11;14) – N (%)** |             |             |             |
| No               | 1.00        |             |             |
| Yes              |             | 0.038       |             |
| Missing          |             |             | 0.038       |

IQR, interquartile range; VMP, bortezomib-melphalan-prednisone; Rd-R, lenalidomide-dexamethasone followed by lenalidomide maintenance; LDH, lactate dehydrogenase; ISS, International Staging System; PS, performance status. *High-risk defined by the presence of either one among del17, t(4;14), t(14;16), detected by FISH;
Table 2. Second-line treatment

|                       | All patients (N=474) | VMP (N=257) | Rd-R (N=217) | p-value |
|-----------------------|----------------------|-------------|--------------|---------|
| **Second-line treatment – N(%)** |                      |             |              |         |
| Yes                   | 296 (62)             | 158 (61)    | 138 (64)     | 0.70    |
| No                    | 178 (38)             | 99 (39)     | 79 (36)      |         |
| **Type of treatment – N (%)** |                      |             |              |         |
| PI                    |                      |             |              |         |
| • Bortezomib          | 144 (49)             | 28 (18)     | 116 (84)     |         |
| • Carfilzomib         | 2 (0)                | 1 (0)       | 1 (0)        |         |
| IMiD                  |                      |             |              |         |
| • Lenalidomide        | 68 (23)              | 68 (43)     | 0 (0)        |         |
| • Thalidomide         | 34 (11)              | 32 (20)     | 2 (1)        |         |
| Other                 | 48 (16)              | 29 (18)     | 19 (14)      |         |

VMP, bortezomib-melphalan-prednisone; Rd-R, lenalidomide-dexamethasone followed by lenalidomide maintenance; PI, proteasome inhibitor; IMiD, immunomodulatory drug.
Table 3. Multivariate Cox models with 3-way interaction between treatment type, age and cytogenetics, adjusted for ISS Stage, Karnofsky, extramedullary disease and age as continuous variable.

| Main analysis                          | PFS          | OS          |
|----------------------------------------|--------------|-------------|
|                                        | HR* (95% CI) | HR* (95% CI)|
| Standard-risk cytogenetics - Age ≤75   | 0.92 (0.67 - 1.27) | 0.83 (0.53 - 1.29) |
| Standard-risk cytogenetics - Age >75   | 0.96 (0.56 - 1.66) | 1.81 (0.94 - 3.49) |
| High-risk cytogenetics - Age ≤75       | 0.75 (0.45 - 1.26) | 0.75 (0.39 - 1.43) |
| High-risk cytogenetics - Age >75       | 0.19 (0.07 - 0.52) | 0.65 (0.21 - 2.04) |
| 3-way interaction-p                    | 0.03         | 0.23        |
| 2-way Cytogenetics interaction-p       | 0.03         | 0.23        |
| 2-way Age interaction-p                | 0.85         | 0.04        |

PFS, progression-free survival; OS, overall survival; ISS, International Staging System; CI, confidence interval. *HR refers to the comparison between VMP vs Rd-R.
**Figure 1.** Subgroup analysis of progression-free survival in the intent-to-treat population for VMP versus Rd-R.

**Figure 2.** Subgroup analysis of overall survival in the intent-to-treat population for VMP versus Rd-R.
SUPPLEMENTARY APPENDIX

Additional methods

Study treatments

In the GIMEMA-MM-03-05 study, 511 patients were enrolled and randomized to receive either nine induction cycles with VMP or VMP plus thalidomide (VMPT) induction followed by bortezomib-thalidomide maintenance (VT). In the EMN01 study, 654 patients were randomized to receive nine induction cycles of either Rd, melphalan-prednisone-lenalidomide (MPR) or cyclophosphamide-prednisone-lenalidomide (CPR); after the induction phase, patients were randomized to receive lenalidomide (R) maintenance with or without prednisone until disease progression or unacceptable toxicity. Ethics committees or institutional review boards at the study sites approved both studies, which were done in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Inclusion and exclusion criteria of the source trials

GIMEMA-MM-03-05

Inclusion criteria:

- Age > 65 years old and not a candidate for stem cell transplant, or younger who refuses or is not eligible for high-dose therapy
- Symptomatic multiple myeloma or asymptomatic multiple myeloma with related organ or tissue damage
- Presence of measurable disease
- Karnofsky performance status (PS) > 60% (see Appendix E)
- Able to read and complete the HRQOL instruments
- Agrees to use an acceptable barrier method for contraception for the duration of the study
- Pretreatment clinical laboratory values within 14 days of randomization:
  - Platelet count ≥ 100x10⁹/L
  - Hemoglobin ≥ 8 g/dL
  - Absolute neutrophil count (ANC) ≥ 1.0x10⁹/L
  - AST ≤ 2.5 times the upper limit of normal
  - ALT ≤ 2.5 times the upper limit of normal
  - Total bilirubin ≤ 1.5 times the upper limit of normal
  - Serum creatinine ≤ 2.5mg/dL
  - Corrected serum calcium <14 mg/dL (<3.5 mmol/L)
- Subjects (or their legally acceptable representatives) must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
- Women of child-bearing potential must agree to use 2 methods of contraception: 1 effective (for example hormonal or tubal ligation) and 1 barrier (for example latex condom, diaphragm) for at least 4 weeks before starting the therapy, during the Treatment Period, and for 4 weeks after the last dose;
- Males must agree to use barrier contraception (latex condoms) when engaging in reproductive activity during the Treatment Period and for 4 weeks after the last dose.
Exclusion criteria:

- Diagnosis of smoldering multiple myeloma or MGUS.
- Diagnosis of Waldenstrom’s disease
- Prior or current systemic therapy for multiple myeloma including steroids (with exception of emergency use of a short course [maximum 4 days] of steroids before randomization or prior or current use of bisphosphonates)
- Radiation therapy within 30 days before randomization
- Plasmapheresis within 30 days before randomization
- Major surgery within 30 days before randomization (Kyphoplasty is not considered major surgery)
- History of allergic reaction attributable to compounds containing boron or mannitol, or to Thalidomide
- Peripheral neuropathy Grade 2 or higher, as defined by National Cancer Institute Common Toxicity Criteria (NCI CTC) 3.0
- Uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis
- Other malignancy within the past 5 years. Exceptions: basal cell or non-metastatic squamous cell carcinoma of the skin, cervical carcinoma in situ or FIGO Stage 1 carcinoma of the cervix
- Concurrent medical condition or disease (e.g., active systemic infection, uncontrolled diabetes, pulmonary disease) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study
- Use of any investigational drugs within 30 days before randomization.
- Pregnant or lactating women. A serum β-hCG pregnancy test must be performed at the Screening visit, for female patients of child-bearing potential. If the test is positive, the patient must be excluded from the study. Confirmation that the patient is not pregnant must be established by a negative serum or urinary pregnancy test with the result obtained 1 day prior to the Baseline visit (or the day of the visit if results are available before drug delivery). A pregnancy test is not required for naturally post-menopausal women (who have not had menses at any time in the preceding 24 consecutive months) or surgically sterilized women (hysterectomy, bilateral ovariectomy, bilateral salpingectomy);
- Patients or partners of patients of reproductive potential:
  - If thalidomide is taken during pregnancy (even as a single dose), it can cause severe birth defects or death of an unborn baby. Thalidomide should never be used by women who are pregnant or could become pregnant whilst taking the drug.
  - Women must not breastfeed whilst taking thalidomide, and for 8 weeks after finishing thalidomide treatment. It is also important that the female partners of male patients do not become pregnant whilst taking thalidomide.
  - Women of child-bearing potential must employ two methods of contraception (at the same time): one of which is highly effective (intra-uterine device (IUD), birth control pills, tubal ligation, or partner’s vasectomy) and another additional method (condom, diaphragm, or cervical cap). These birth control methods must be used for at least 4 weeks before starting thalidomide therapy, during thalidomide therapy and for at least 4 weeks after thalidomide therapy has stopped. Women who have had a hysterectomy or have been postmenopausal for at least 24 consecutive months do not have to use the described contraceptive measures.
  - A serum β-hCG pregnancy test must be performed at the screening visit, for female patients of child-bearing potential. If the test is positive, the patient must be excluded from the study. A serum or urinary pregnancy test will be repeated 1 day prior to the baseline visit, every 4
weeks during treatment (1 day before each visit), at the End of Treatment visit, and at the Confirmation of PD visit. For female patients with irregular periods, a serum or urinary pregnancy test must be performed every 2 weeks during treatment. The pregnancy test may only be performed on the day of the visit if results are available before drug delivery.

- As thalidomide is present in semen, all male patients should use a condom during intercourse, even if they have undergone a prior vasectomy. This contraceptive measure must be employed whilst taking the drug and for 4 weeks after stopping treatment. Male patients should inform their partners of the risk of exposure and consider practicing a second method of birth control in addition to condom use.
- Patients must never donate sperm or blood whilst being treated with thalidomide and for 8 weeks after finishing treatment with thalidomide.

**EMN01**

**Inclusion criteria:**

- Patient is, in the investigator(s) opinion, willing and able to comply with the protocol requirements.
- Patient has given voluntary written informed consent before performance of any study related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to their future medical care.
- Patient is 65 years old or older at the time of signing the informed consent or younger patients not candidate to high dose therapy.
- Female patient is either post-menopausal or surgically sterilized or, if at child-bearing potential, must:
  - understand that the study medication could have an expected teratogenic risk
  - Agree to use, and be able to comply with, effective contraception without interruption, 4 weeks before starting study drug, throughout study drug therapy (including dose interruptions) and for 4 weeks after the end of study drug therapy, even if she has amenorrhea. This applies unless the subject commits to absolute and continued abstinence confirmed on a monthly basis. The following are effective methods of contraception:
    - Implant
    - Levonorgestrel-releasing intrauterine system (IUS)
    - Medroxyprogesterone acetate depot
    - Tubal sterilization
    - Sexual intercourse with a vasectomized male partner only; vasectomy must be confirmed by two negative semen analyses
    - Ovulation inhibitory progesterone-only pills (i.e., desogestrel)
    - Combined oral contraceptive pills are not recommended. If a subject was using combined oral contraception, she must switch to one of the methods above. The increased risk of VTE continues for 4 to 6 weeks after stopping combined oral contraception.
    - Prophylactic antibiotics should be considered at the time of insertion particularly in patients with neutropenia due to risk of infection
  - Agree to have a medically supervised pregnancy test with a minimum sensitivity of 25 mIU/ml not more than 3 days before the start of study medication once the subject has been on effective contraception for at least 4 weeks. This requirement also applies to women of childbearing potential who practice complete and continued abstinence.
Agree to have a medically supervised pregnancy test every 4 weeks including 4 weeks after the end of study treatment, except in the case of confirmed tubal sterilization. These tests should be performed not more than 3 days before the start of next treatment. This requirement also applies to women of childbearing potential who practice complete and continued abstinence.

- Male subjects must:
  - Agree to use condoms throughout study drug therapy, during any dose interruption and for one week after cessation of study therapy if their partner is of childbearing potential and has no contraception.
  - Agree not to donate semen during study drug therapy and for one week after end of study drug therapy.

- All subjects must:
  - Agree to abstain from donating blood while taking study drug therapy and for one week following discontinuation of study drug therapy.
  - Agree not to share study medication with another person and to return all unused study drug to the investigator.

- Patient was previously diagnosed with symptomatic MM based on standard criteria, and has measurable disease, defined as follows:
  - Secretory myeloma: any quantifiable serum monoclonal protein value (generally, but not necessarily, greater than 1 g/dL of IgG M-Protein and greater than 0.5 g/dL of IgA M-Protein) and, where applicable, urine light-chain excretion of >200 mg/24 hours;
  - Non-secretory myeloma: > 30% plasma cells in the bone marrow and at least one plasmacytoma > 2 cm as determined by clinical examination or applicable radiographs (i.e., MRI or CT scan).

- Patient has a baseline bone marrow sample available for cytogenetics, that will be processed and eventually centralized within each country.
- Patient has a Karnofsky performance status ≥ 60%.
- Patient has a life-expectancy > 6 months
- Patients must have an adequate cardiac function
- Patients must have adequate pulmonary function
- Patient has the following laboratory values within 14 days before Baseline (day 1 of the Cycle 1):
  - Platelet count ≥ 75 x 10^9/L without transfusion support within 7 days before the test.
  - Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L without the use of growth factors.
  - Corrected serum calcium ≤ 14 mg/dL (3.5 mmol/L).
  - Aspartate transaminase (AST): ≤ 2.5 x the upper limit of normal (ULN).
  - Alanine transaminase (ALT): ≤ 2.5 x the ULN.
  - Total bilirubin: ≤ 1.5 x the ULN.
  - Calculated or measured creatinine clearance: ≥ 30 mL/minute.

**Exclusion criteria:**

- Previous treatment with anti-myeloma therapy (does not include radiotherapy, bisphosphonates, or a single short course of steroid; ≤ to the equivalent of dexamethasone 40 mg/day for 4 days).
- Any serious medical condition, including the presence of laboratory abnormalities, which places the subject at an unacceptable risk if he or she participates in this study or confounds the experimental ability to interpret data from the study.
- Pregnant or lactating females.
- Prior history of malignancies, other than multiple myeloma, unless the subject has been free of the disease for ≥ 3 years. Exceptions include the following: Basal cell carcinoma of the skin, Squamous
cell carcinoma of the skin, Carcinoma in situ of the cervix, Carcinoma in situ of the breast, Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b).

**Procedures**

Patients in the VMP arm of the GIMEMA-MM-03-05 study received nine 6-week induction cycles of intravenous bortezomib at 1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9; oral melphalan at 9mg/m² on days 1 to 4; oral prednisone at 60 mg/m² on days 1 to 4. The protocol was amended after the inclusion of the first 139 patients, and the schedule was changed to nine 5-week cycles and bortezomib dose was modified to 1.3 mg/m² on days 1, 8, 15, and 22 during cycles 1 to 9. Patients in the Rd-R arm of the EMN01 study received nine 4-week induction cycles of lenalidomide at 25 mg daily on day 1 to 21; and dexamethasone at 40 mg in patients below 75 years or 20 mg in patients over 75 years, on days 1, 8, 15 and 22. Afterwards, patients were randomly assigned to receive maintenance treatment with lenalidomide alone at 10 mg on days 1 to 21 every 28 days or in combination with prednisone at 25 mg every other day continuously, until disease progression or intolerance (Rd-R).

**Survival outcomes definition**

Progression-free survival (PFS) was calculated from the date of diagnosis to the date of progression or death or the date the patient was last known to be in remission. Overall survival (OS) was calculated from the date of diagnosis to the date of death or the date the patient was last known to be alive.
**Figure S1.** Subgroup analysis of Progression-free survival for VMP versus Rd in the single high-risk cytogenetic subgroups, adjusted for age, ISS Stage, Karnofsky and extramedullary disease.

| Subgroup | HR (95% CI) | Interaction-p |
|----------|-------------|---------------|
| Overall  | 0.81 (0.65 - 1.01) | |
| del(17p) |              |               |
| no       | 0.87 (0.67 - 1.13) | 0.25          |
| yes      | 0.59 (0.32 - 1.09) |               |
| missing  | 0.76 (0.47 - 1.24) |               |
| t(4;14)  |              |               |
| no       | 0.90 (0.69 - 1.17) | 0.08          |
| yes      | 0.50 (0.27 - 0.93) |               |
| missing  | 0.77 (0.47 - 1.25) |               |
| t(14;16) |              |               |
| no       | 0.87 (0.68 - 1.11) | 0.21          |
| yes      | 0.35 (0.09 - 1.42) |               |
| missing  | 0.74 (0.46 - 1.19) |               |

**Figure S2.** Subgroup analysis of Overall survival for VMP versus Rd in the single high-risk cytogenetic subgroups, adjusted for age, ISS Stage, Karnofsky and extramedullary disease.

| Subgroup | HR (95% CI) | Interaction-p |
|----------|-------------|---------------|
| Overall  | 0.85 (0.63 - 1.14) | |
| del(17p) |              |               |
| no       | 0.99 (0.70 - 1.40) | 0.62          |
| yes      | 0.81 (0.38 - 1.71) |               |
| missing  | 0.52 (0.29 - 0.95) |               |
| t(4;14)  |              |               |
| no       | 1.01 (0.71 - 1.42) | 0.46          |
| yes      | 0.74 (0.35 - 1.56) |               |
| missing  | 0.52 (0.29 - 0.95) |               |
| t(14;16) |              |               |
| no       | 0.98 (0.70 - 1.36) | 0.74          |
| yes      | 0.73 (0.13 - 4.05) |               |
| missing  | 0.51 (0.29 - 0.91) |               |
**Figure S3.** Subgroup analysis of Progression-free survival in the intent-to-treat population for VMP versus Rd with multiple imputation

| Subgroup          | HR (95% CI)       | Interaction-p |
|-------------------|-------------------|---------------|
| Overall           | 0.85 (0.69 - 1.04)|               |
| **Cytogenetics**  |                   |               |
| standard-risk     | 1.01 (0.78 - 1.30)| 0.02          |
| high-risk         | 0.53 (0.34 - 0.82)|               |
| **Age**           |                   |               |
| ≤75               | 0.83 (0.65 - 1.05)| 0.86          |
| >75               | 0.86 (0.57 - 1.29)|               |

Favors VMP  Favors Rd-R

**Figure S4.** Subgroup analysis of Overall survival in the intent-to-treat population for VMP versus Rd with multiple imputation

| Subgroup          | HR (95% CI)       | Interaction-p |
|-------------------|-------------------|---------------|
| Overall           | 0.86 (0.66 - 1.13)|               |
| **Cytogenetics**  |                   |               |
| standard-risk     | 0.97 (0.69 - 1.37)| 0.26          |
| high-risk         | 0.66 (0.39 - 1.14)|               |
| **Age**           |                   |               |
| ≤ 75              | 0.72 (0.52 - 0.99)| 0.05          |
| >75               | 1.29 (0.79 - 2.08)|               |

Favors VMP  Favors Rd-R
Table S1. Multivariate Cox models with multiple imputation method with 3-way interaction between treatment type, age and cytogenetics, adjusted for ISS Stage, Karnofsky, extramedullary disease and age as continuous variable.

| Multiple imputation analysis | PFS HR* (95% CI) | OS HR* (95% CI) |
|-----------------------------|------------------|-----------------|
| Standard-risk cytogenetics - Age ≤75 | 0.89 (0.66 - 1.19) | 0.76 (0.51 - 1.13) |
| Standard-risk cytogenetics - Age >75 | 1.25 (0.78 - 2.01) | 1.61 (0.89 - 2.93) |
| High-risk cytogenetics - Age ≤75 | 0.69 (0.41 - 1.16) | 0.64 (0.34 - 1.21) |
| High-risk cytogenetics - Age >75 | 0.26 (0.11 - 0.62) | 0.75 (0.27 - 2.05) |
| 3-way interaction-p | 0.03 | 0.41 |
| 2-way Cytogenetics interaction-p | 0.02 | 0.26 |
| 2-way Age interaction-p | 0.86 | 0.05 |

PFS, progression-free survival; OS, overall survival; ISS, International Staging System; CI, confidence interval. *HR refers to the comparison between VMP vs Rd-R.