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Superior outcomes and high-risk features with carfilzomib, lenalidomide, and dexamethasone combination therapy for patients with relapsed and refractory multiple myeloma: results of the multicenter KMMWP2201 study

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Running title: KRd in Asian RRMM patients

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The authors have no competing financial interest to declare.

Authorship contributions
Study design: Ji Hyun Lee, and Sung-Hyun Kim. Patient enrollment and data collection: Ji Hyun Lee, Chang-Ki Min, Sung-Soo Park, Jae-Cheol Jo, Yoo Jin Lee, Jin Seok Kim, Hyun-Seok Uhm, Jong heon Jung, Joon Ho Moon, Hee Jeong Cho, Myung-won Lee, Sung-Soo Yoon, Ja Min Byun, Jae Hoon Lee, Je-Jung Lee, Sung-Hoon Jung, Ho-Jin Shin, Do Young Kim, Jun Ho Yi, Seung-Shin Lee, Young Rok Do, Dok Hyun Yoon, Hyungwoo Cho, Won Sik Lee, Ho Sup Lee, Jieun Uhm, Hyo Jung Kim, Hee Ryeong Jang, Sung-Hyun Kim, and Kihyun Kim. Data analysis: Ji Hyun Lee and Jimin Choi. Paper writing: Ji Hyun Lee, Sung-Hyun Kim, and Kihyun Kim. Paper revisions: All authors.

Data Sharing Statement For original data, please contact Ji Hyun Lee, hidrleejh@dau.ac.kr.

Abstract

Carfilzomib, lenalidomide, and dexamethasone (KRd) combination therapy improves the survival of patients with relapsed and/or refractory multiple myeloma (RRMM). Nonetheless, evidence on the use of KRd in Asian populations remains scarce. Accordingly, this study aimed at investigating this regimen's efficacy in a large group of patients. This retrospective study included patients with RRMM who were treated with KRd at 21 centers between February 2018 and October 2020. Overall, 364 patients were included (median age: 63 years). The overall response rate was 90% in response-evaluable patients, including 69% who achieved a very good partial response or deeper responses. With a median follow-up duration of 34.8 months, the median progression-free survival (PFS) was 23.4 months and overall survival (OS) was 59.5 months. Among adverse factors affecting PFS, high-risk cytogenetics, extramedullary disease, and doubling of monoclonal protein within 2 to 3 months prior to start of KRd treatment significantly decreased PFS and overall survival (OS) in multivariate analyses. Patients who underwent post-KRd stem cell transplantation (i.e.delayed transplant) showed prolonged PFS and OS. Grade 3 or higher adverse events (AEs) were observed in 56% of the patients, and non-fatal or fatal AE's that resulted in discontinuation of KRd were reported in 7% and 2% of patients, respectively. Cardiovascular toxicity was comparable to that reported in the ASPIRE study. In summary, KRd was effective in a large real-world cohort of patients with RRMM with long-term follow-up. These findings may further inform treatment choices in the treatment of patients with RRMM.

Keywords, Carfilzomib, Lenalidomide, Relapsed and refractory multiple myeloma, High-risk, Asia

Introduction

Antimyeloma therapy has progressed over the last decade with the sequential introduction of second-generation proteasome inhibitors (PIs), monoclonal antibodies (mAbs), bispecific antibodies (BiTEs), and chimeric antigen receptor T-cell therapies[1-7]. Among these, carfilzomib, a second-generation irreversible epoxyketone-based irreversible PI, in combination with lenalidomide and dexamethasone, dramatically improved the treatment outcome of relapsed and/or refractory multiple myeloma (RRMM) [1]. Its efficacy has been confirmed in the phase III ASPIRE trial, which led to global regulatory approval. Subsequently, prospective clinical trials adopted carfilzomib, lenalidomide, and dexamethasone (KRd) in the upfront setting and it has since been used as the backbone for various combination regimens including mAbs for patients with multiple myeloma (MM) with high-risk genetic features as well as for patients with RRMM[8-11].

Despite plenty of evidence on the use of the KRd regimen to treat MM, the effectiveness and toxicity of the KRd triplet combination regimen have not been verified in a large real-world population of Asian patients with RRMM; in particular, the ASPIRE trial had poor cross-ethnic generalizability[12]. In addition, a previous phase I Japanese study, which had strict eligibility criteria, and a retrospective Korean study, which included 25% of lenalidomide-refractory patients, showed shorter progression-free survival (PFS) than that showed by the ASPIRE study after a limited duration of follow-up[13, 14]. Furthermore, carfilzomib and dexamethasone doublet therapy was associated with an elevated risk of grade 3 or higher adverse events (AE)s in an Asian study cohort[15]. However, the efficacy and toxicity of KRd combination therapy in a large cohort of patients with RRMM with long-term follow-up remains to be established.

To address this issue, our study aimed to examine the overall effectiveness and adverse event profile of KRd combination therapy in real-world patients with RRMM and further analyze the impact of their clinical characteristics, focusing in particular on high-risk factors that might adversely influence the efficacy of KRd therapy in this setting.

Methods

Retrospective data of 381 patients treated with carfilzomib (Kyprolis®, Amgen Inc.), lenalidomide, and dexamethasone combination therapy for RRMM at 21 participating centers for the Korean Multiple myeloma working party (KMMWP), between February 2018 and October 2020, were collected. During this study period, KRd was the sole lenalidomide-based triplet therapy reimbursed amongst newer agent combination regimens. Among these patients, 17 were excluded from analysis because of ineligibility for the treatment commencement date and missing information on first-line therapy. The data cutoff date for all patients was March 2023. The primary objective of this study was to evaluate the effectiveness of KRd by examining the overall progression-free survival (PFS). Secondary objectives were examining PFS according to high-risk factors, overall survival (OS), overall response rate (ORR), and AEs. High-risk factors were defined by the presence of an International Staging System (ISS) stage III, revised ISS (R-ISS) stage III, high-risk cytogenetics at the time of initial diagnosis, extramedullary disease (EMD), symptomatic disease (hypercalcemia, renal failure, anemia, and bone lesions), doubling of the M protein within 2-3 months of KRd therapy, the presence of

amyloidosis, and plasma cell leukemia (PCL) at the time of treatment. High-risk cytogenetics were indicated when the results were positive for t(4;14), t(14;16), and del (17p) by G-banding or fluorescence in situ hybridization (FISH), based on recommendations from the International Myeloma Working Group (IMWG) consensus panel 2[16]. Demographic data, baseline characteristics of MM, effectiveness, and AE of KRd therapy were obtained by a meticulous review of electronic medical records, according to a protocol approved by the Institutional Review Board (DAUHIRB-22-081) of each participating hospital, in accordance with the Declaration of Helsinki. This study was approved by the Scientific Committee of KMMWP (KMM2201) (For detailed description, see supplementary methods).

1. Statistical analysis

The baseline characteristics were summarized using descriptive statistics. The ORR was defined as the percentage of patients who achieved a partial response (PR) or better[17]. Relative dose intensity (RDI) was calculated as the dose divided by the planned dosage per cycle. Univariate analysis of the binary factors affecting the ORR was conducted using the chi-square test, and the p value was 2-sided. The ORR was illustrated using GraphPad Prism (version 9.4.1; GraphPad Software, San Diego, CA, USA) according to the tested variables. Additionally, PFS was calculated from the first date of KRd administration to the date of disease progression, death, or censoring. Moreover, PFS2 was defined from the date of KRd to the date of myeloma progression on the next-line treatment or death from any cause or censoring. Furthermore, OS was estimated from the first date of KRd to the date of death or censoring. Kaplan–Meier curves were used to analyze PFS, PFS2, and OS, and the differences between variables were compared using the log-rank test. Multivariate survival analysis of PFS and OS were performed using the Cox proportional hazards model. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS 28.0 (IBM Corp. Version 28.0. Armonk, NY) and R 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria. URL: https://www. R-project. org/)

Results

1. Baseline characteristics

The baseline patient demographics, disease, and treatment data are shown in Table 1. Three hundred sixty-four patients were treated with KRd combination therapy for RRMM. The median patient age was 63 years (range, 28–85 years). Two hundred and thirteen patients (59%) had baseline features that did not meet the eligibility criteria for the ASPIRE trial. Supplementary Figure 1 illustrates the trial-ineligibility in this study, of which the biggest reasons for exclusion was bortezomib refractoriness (33%), followed by creatinine clearance < 50 mL/min (23%), platelet < 50,000/uL (6%), and an eastern cooperative group performance status (ECOG PS) of ≥ 3 (6%). Cytogenetic data were available for 77% of the analyzed patients, of which 98 (27%) had one or more high-risk cytogenetics, of whom 18 had either two high-risk cytogenetics, and two had all three high-risk karyotypes. Extramedullary plasmacytomas were observed in 87 (24 %) patients at the time of KRd treatment and included 32 patients (9%) with soft tissue plasmacytomas. The median number of previous lines of therapy was one (range, 1–4), with 4% of the patients having received more than two lines of therapy.

Two hundred and one (55%) patients had been previously treated with autologous stem cell transplantation (auto-SCT), and four patients had received allogeneic stem cell transplantation (allo-SCT). Bortezomib and thalidomide were used in 90% and 66% of patients, respectively, and refractoriness to bortezomib and thalidomide was observed in 33% and 25% of patients, respectively.

2. Overall response after carfilzomib-lenalidomide-dexamethasone treatment

The median number of treatment cycles was 13 (range, 1–55). A total of 147 patients (40%) were maintained on lenalidomide and dexamethasone or lenalidomide alone after 18 cycles of carfilzomib. The median RDI for carfilzomib, lenalidomide, and dexamethasone were 1.00 (range, 0.05–1.00), 0.82 (range, 0.01–1.00), and 0.77 (range, 0.06–1.00), respectively. Response was evaluable in 97% of the patients, and ORR was observed in 90% of the response-evaluable patients. Additionally, very good partial response (VGPR), complete response (CR), and stringent CR (sCR) were achieved in 24%, 31%, and 6% of the patients, respectively. Among the 62 patients who were evaluated for minimal residual disease (MRD) using the EuroFlow standard operation procedure, 36% (22 of 62) were Flow MRD-negative, which accounted for 6% of the responses. A detailed summary of the factors affecting ORR is illustrated in Supplementary Figure 2. Among the baseline patient-, and treatment-related factors, older age (≥ 65 years, ≥ 70 years, and ≥ 75 years), ECOG PS ≥3, creatinine clearance (CCr) ≥ 50 mL/min, and previous auto-SCT or bortezomib treatment did not decrease ORR, however, a platelet count <50,000/μL, bortezomib-refractoriness, bortezomib response duration < 12 months, previous thalidomide treatment, thalidomide refractoriness, and thalidomide response duration < 12 months decreased the ORR. High-risk disease-related factors, such as the existence of EMD, doubling of M protein within 2 to 3 months of KRd therapy, symptomatic MM, amyloidosis, and plasma cell leukemia at the time of KRd treatment did not significantly impact the response to KRd therapy, but ISS III (ISS I and II vs. III; 92% vs. 84%, P=0.0306), R-ISS III (R-ISS I and II vs. III; 92% vs. 78%, P=0.0023), and high-risk cytogenetics (standard vs. high-risk cytogenetics; 93% vs. 80%, P=0.0041) significantly decreased ORR.

3. Survival data and analysis of factors affecting PFS and OS

By the date of analysis, 284 (78%) patients had discontinued treatment. The most common cause of treatment termination was disease refractoriness during KRd treatment (52%), followed by AEs (9%), transplantation (7%; 21 auto-SCT and 4 allo-SCT), and death from any cause (4%). After a median follow-up duration of 34.8 months (range, 0.00–61.5 months), PFS was 23.4 months (95% CI, 19.0-26.4 months) and OS was 69.5 months with a 3-year OS of 64.7% (95% confidence interval, CI, 59.8%-70%) (Figure 1A and B). As listed in Table 3, among the high-risk factors that significantly affected survival as shown by univariate analysis, multivariate analysis showed that high-risk cytogenetics, EMD, and doubling of M protein within 2–3 months of KRd therapy significantly shortened the PFS and OS (standard-risk vs. high-risk, P=0.0077; no EMD vs. presence of EMD, P=0.0461; no doubling of M protein within 2-3months vs. doubling of M protein within 2-3 months, P=0.0257). Salvage chemotherapy was administered to 54% of the patients (Supplementary Table 1). Patients who received consolidative SCT (first SCT 40% and second SCT 60%) after a median of six

cycles (range, 2-22) of KRd therapy showed a significantly improved PFS (SCT vs. no SCT, P=0.0259) and OS (SCT vs. no SCT, P=0.0005), and salvage chemotherapy with newer target agents showed a prolonged PFS2 after KRd therapy (Figure 2A-D). Clinical trial eligibility significantly affected PFS and OS (Supplementary Figure 3A and B). Among the baseline patient characteristics, presence of platelets < 50,000/μL significantly shortened PFS and OS, and patients aged 65 years or older had poorer OS, as shown by multivariate analysis (Supplementary Table 2). Among the treatment-related factors, a bortezomib response duration > 12 months significantly prolonged PFS and OS as shown by the multivariate analysis (Supplementary Table 3).

4. Toxicity profile after KRd therapy

Table 4 summarizes the overall AE profiles of the patients. Of them, 317 patients (87%) experienced any AEs, of which grade 3 or higher toxicities were observed in 56%. Additionally, AE resulted in dose reductions of carfilzomib, lenalidomide, and dexamethasone in 27%, 38%, and 39% of the patients, respectively, and discontinuation of the drug before the scheduled cycles for carfilzomib in 12% of the patients, and in 12%, and 13% of the patients for lenalidomide and dexamethasone, respectively. Grade 3 or higher cardiovascular AEs, such as dyspnea, acute kidney injury, congestive heart failure (CHF), arrhythmias, deep vein thrombosis, hypertension, and ischemic heart disease, were reported in less than 5% of patients. Secondary primary malignancy (SPM) occurred in seven patients (2%). Fatal AEs occurring during the KRd therapy were reported in six patients: three cases of secondary malignancies, two case of pneumonia, and one case of ventricular fibrillation associated with CHF (Supplementary Table 4). Detailed information on the AEs reported during or after the KRd therapy is provided in Supplementary Table 5. Neutropenia was the most common grade 3 or higher AE (34%), which resulted in ≥ grade 3 non-fatal neutropenic fever in 3% of the patients. The most common grade 3 or higher non-hematologic AEs was infection (12%), followed by fatigue (9%). Ten percent of the patients suffered from acute kidney injury (AKI), especially in patients with significantly lower CCr compared with those that did not experience further AKI after KRd treatment (AKI vs. no AKI = mean ± standard deviation, 60.36 ± 22.11 mL/min vs. 93.67 ± 66.74 mL/min, respectively, P=0.0041) (Supplementary Figure 4).

Discussion

Despite recent advances in novel immunotherapies, triplet combination therapy remains a mainstay of treatment for patients with RRMM globally[18]. The landmark phase III ASPIRE trial examining KRd therapy included only one Asian patient and there is a clear scarcity of data on using KRd therapy in the Asia-Pacific region, thus making a real-world study on KRd conducted in a large cohort of potential importance[1]. This study evaluated 364 Asian patients with RRMM who were treated with the KRd regimen in real-world clinical practice. The ORR was 90%, with a VGPR or higher response of 69%. After a median follow-up of 35 months, the median PFS and OS rates were 23 and 60 months, respectively. Table 5 summarizes the clinical data on KRd therapy, which includes prospective studies and enriches recent retrospective studies in large study populations and Asian cohorts[1, 13, 19-22]. Although this study included 59% of the patients who were ineligible for the ASPIRE study and those

with high-risk cytogenetics and EMD, the PFS and ORR were comparable and/or favorable with those of previous prospective and retrospective analyses, with the OS proving longer than that seen in the pivotal phase III study (ASPIRE). There is also a large gap in the data, because of the nature and status of government reimbursement in the Republic of Korea. Specifically, this might have affected the difference between the outcome of this study and that of a previous report of 55 patients who were treated with KRd at their own expense[14]. In the current study, patients were treated in an earlier line of therapy, most patients were lenalidomide-naïve, and had better bone marrow reserve than that of patients who were treated with carfilzomib in combination with Rd as one of the last treatment options. This difference indicates that using effective therapeutic options as an earlier line of therapy favorably affects overall outcome, which is especially influenced by treatment cost in real-world clinical practice and across global healthcare systems.

Notably, this study focused on the performance of KRd therapy according to the aggressiveness of the disease, presence of EMD, doubling of M protein within 2–3 months, symptomatic MM, plasma cell leukemia, and presence of amyloidosis at the time of relapse or refractoriness, as well as ISS, R-ISS, and high-risk cytogenetics at diagnosis of MM, which were included in 24%, 12%, 73%, 2%, 1%, 35%, 21%, and 27% of the patients, respectively. Multivariate analysis revealed that high-risk cytogenetics, the presence of EMD, and doubling of M protein levels within 2–3 months significantly affected PFS and OS. The poor prognostic impact of high-risk cytogenetics is consistent with previous single-arm KRd studies[19, 20]. EMD at disease relapse has traditionally been an uncontrollable situation of RRMM as per previous reports, which showed approximately 4–8 months of PFS and approximately 12 months of OS [22, 23]. Although EMD was a poor prognostic factor in this study, the ORR was 83% with a PFS of 14 months and OS of 36 months. Recently, bispecific antibody therapies with different targets have shown promising results, with an ORR of 83% in patients with EMD[24]. Hence, it can be inferred that a new combination therapy, especially one involving bispecific antibody therapies with KRd or similar as primary therapy, might be promising for treating patients with EMD. In terms of the doubling of the M protein within 2-3 months at the time of relapse, the ORR was 81%, and the PFS and OS were 14 and 38 months, respectively. This change in the M protein has been suggested to be a high-risk factor but has not been studied in a large cohort of patients in the new agent era[25]. To the best of our knowledge, this is the first study to show that a rapid increase in M protein levels is an aggressive tumor-related factor in patients with RRMM treated with Rd-based triplet combination therapy. This also suggests that this clinical feature necessitates further investigation and additional study of next generation novel therapy.

Prior therapies and the quality of response to previous treatments significantly affected the response to KRd therapy, among which a bortezomib response duration longer than 12 months was the sole factor that had a significant impact on longer PFS and OS in multivariate analysis. The outcome of KRd therapy according to prior bortezomib refractoriness has been controversial across prospective and retrospective studies[14, 19, 22], which may have been affected by the limited number of patients included. Although we could not make a formal comparison with other Rd-based triplet regimens because of the different characteristics of the included patients, we suggest that the KRd regimen has the greatest benefit in patients who have a bortezomib response duration that is longer than 12

months; additionally, there may be a limited impact of thalidomide-refractoriness or response duration to thalidomide on the effectiveness of KRd treatment, recognizing that thalidomide use has diminished considerably with the use of lenalidomide now as part of upfront therapy and maintenance across most health care jurisdictions[26-28].

Approximately 6% of the patients could be consolidated with high-dose chemotherapy with stem cell rescue, either in their first or second transplantation after a median six cycles of KRd treatment, which significantly prolonged PFS and OS. This result is in line with findings from previous retrospective studies that have evaluated the effect of auto-SCT after the salvage KRd regimen either as a first or second auto-SCT and suggested a potential beneficial effect of consolidative auto-SCT in available patients, although the number of patients in our study is relatively small, so this has to be interpreted with caution[29, 30]. In terms of salvage treatments affecting PFS2, the incorporation of mAbs or new classes of drugs into the next line of therapy has been more effective than conventional agents or pomalidomide-based combination therapies without newer agents in this study. Based on these results, the recent development of immunotherapies and their combination regimens may significantly benefit patients who progress after KRd therapy and, in a broad sense, those who are lenalidomide-refractory. Importantly, the use of pomalidomide-based therapy in early relapse has become increasingly established, with pomalidomide combination strategies incorporating dexamethasone, PIs and mAbs showing substantial efficacy, and obtaining various regulatory approvals accordingly[31-34]. Nonetheless, access to pomalidomide in combination with newer agents remains constrained in many countries globally, making our findings of continued relevance.

Overall, there were no unexpected AEs in this large real-world cohort of patients with RRMM. Overall incidence of the toxicity Toxicities of the KRd regimen were observed in most of the patients, but grade 3 or higher AEs were reported in 56% of the study population. The incidence of grade 3 or higher AE was lower in comparison with ASPIRE study possibly due to active dose reductions and use of KRd in earlier line of therapy for vast majority of patients. Fatal AEs did not increase compared to those in the phase III trial. Hematologic AEs were more common than non-hematologic AEs and were mostly manageable. Infections were observed in 21% of the patients, but grade 3 or higher infections occurred in 11% of the patients, which led to death in two patients. A previous retrospective Korean study on KRd before imbursement has reported a high rate of ≥ grade 3 infections (20%). The reduced incidence of severe infections in this study might reflect the adoption of the KRd regimen as an earlier line of therapy using more cautious monitoring and prophylaxis for infectious complications than those used in the previous report. The slightly higher incidence of AKI in this study than that in the ASPIRE trial is in line with previous studies' findings[14,35]. Patients who experienced AKI in this study had a lower mean CCr than that had by those who did not experience AKI, which suggests that physicians should be alert choosing a carfilzomib-based regimen for treating RRMM patients with renal failure. Although this study included patients with ongoing cardiovascular risk factors, grade 3 or higher cardiovascular AEs did not increase compared to the pivotal phase III trial ASPIRE. During KRd treatment, seven patients (2%) had secondary primary SPM, none of whom had related preexisting cancers. The mechanism of SPM in MM is complex and precise mechanisms continue to be evaluated[28,36], but there was no correlation between previous alkylator exposure or transplantation

and SPM evolution in this study, although the numbers are small limiting any meaningful interpretation. To the best of our knowledge, this is the first study to analyze the detailed toxicity data of KRd in such a large real-world population with RRMM, which confirmed a tolerability profile comparable to that of previous studies.

In conclusion, the use of carfilzomib in combination with lenalidomide and dexamethasone proved effective with a manageable and expected safety profile when treating a large population of Asian patients with RRMM. Factors reflecting aggressiveness of disease, such as high-risk cytogenetics at diagnosis of MM, EMD, and doubling of the M protein within 2–3 months of relapse and/or refractory status, were associated with decreased PFS and OS in patients treated with KRd therapy. In aggregate, these findings may inform future therapeutic advances and direct treatment choices in the management of patients with RRMM. Additionally, our study also confirms that patients with RRMM and both high-risk laboratory and clinical features require further investigation with novel therapeutics to provide improved outcome.

References

1. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015;372(2):142-152.
2. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398(10297):314-324.
3. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375(14):1319-1331.
4. Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med. 2023;29(9):2259-2267.
5. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2015;373(7):621-631.
6. Moreau P, Masszi T, Grzasko N, et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;374(17):1621-1634.
7. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2021;384(8):705-716.
8. Costa LJ, Chhabra S, Medvedova E, et al. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone With Minimal Residual Disease Response-Adapted Therapy in Newly Diagnosed Multiple Myeloma. J Clin Oncol. 2022;40(25):2901-2912.
9. Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol. 2020;21(10):1317-1330.
10. Leypoldt LB, Besemer B, Asemissen AM, et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in front-line treatment of high-risk multiple myeloma: interim analysis of the GMMG-CONCEPT trial. Leukemia. 2022;36(3):885-888.
11. Roussel M, Lauwers-Cances V, Wuilleme S, et al. Up-front carfilzomib, lenalidomide, and dexamethasone with transplant for patients with multiple myeloma: the IFM KRd final results. Blood. 2021;138(2):113-121.
12. Richardson PG, San Miguel JF, Moreau P, et al. Interpreting clinical trial data in multiple myeloma: translating findings to the real-world setting. Blood Cancer J. 2018;8(11):109.
13. Sugiura I, Suzuki K, Ri M, et al. Final results of a phase I study of carfilzomib, lenalidomide, and dexamethasone for heavily pretreated multiple myeloma. Int J Hematol. 2020;111(1):57-64.
14. Lee JH, Park Y, Kang KW, et al. Carfilzomib in addition to lenalidomide and dexamethasone in Asian patients with RRMM outside of a clinical trial. Ann Hematol. 2021;100(8):2051-2059.
15. Takezako N, Shibayama H, Handa H, et al. Once-weekly vs. twice-weekly carfilzomib dosing in a subgroup of Japanese relapsed and refractory multiple myeloma patients from a randomized phase 3 trial (A.R.R.O.W.) and comparison with ENDEAVOR. Int J Hematol. 2021;113(2):219-230.
16. Munshi NC, Anderson KC, Bergsagel PL, et al. Consensus recommendations for risk

stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. Blood. 2011;117(18):4696-4700.

17. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.

18. Lee JH, Kim SH. Treatment of relapsed and refractory multiple myeloma. Blood Res. 2020;55(S1):S43-S53.

19. Antonioli E, Pilerci S, Attucci I, et al. Carfilzomib, lenalidomide, and dexamethasone in relapsed refractory multiple myeloma: a prospective real-life experience of the Regional Tuscan Myeloma Network. Front Oncol. 2023;13:1162990.

20. Martino EA, Conticello C, Zamagni E, et al. Carfilzomib combined with lenalidomide and dexamethasone (KRd) as salvage therapy for multiple myeloma patients: italian, multicenter, retrospective clinical experience with 600 cases outside of controlled clinical trials. Hematol Oncol. 2022;40(5):1009-1019.

21. Leleu X, Katodritou E, Kuehr T, et al. Real-world use of carfilzomib combined with lenalidomide and dexamethasone in patients with multiple myeloma in Europe and Israel. EJHaem. 2023;4(1):174-183.

22. Kawaji-Kanayama Y, Kobayashi T, Muramatsu A, et al. Prognostic impact of resistance to bortezomib and/or lenalidomide in carfilzomib-based therapies for relapsed/refractory multiple myeloma: The Kyoto Clinical Hematology Study Group, multicenter, pilot, prospective, observational study in Asian patients. Cancer Rep (Hoboken). 2022;5(2):e1476.

23. Blade J, Beksac M, Caers J, et al. Extramedullary disease in multiple myeloma: a systematic literature review. Blood Cancer J. 2022;12(3):45.

24. Cohen YC, Morillo D, Gatt ME, et al. First results from the RedirecTT-1 study with teclistamab (tec) + talquetamab (tal) simultaneously targeting BCMA and GPRC5D in patients (pts) with relapsed/refractory multiple myeloma (RRMM) [abstract]. J Clin Oncol. 2023;41(16_suppl):8002.

25. Sonneveld P. Management of multiple myeloma in the relapsed/refractory patient. Hematology Am Soc Hematol Educ Program. 2017;2017(1):508-517.

26. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1770-1781.

27. 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.

28. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma. N Engl J Med. 2022;387(2):132-147.

29. Baertsch MA, Fougereau M, Hielscher T, et al. Carfilzomib, Lenalidomide, and Dexamethasone Followed by Salvage Autologous Stem Cell Transplant with or without Maintenance for Relapsed or Refractory Multiple Myeloma. Cancers (Basel). 2021;13(18):4706.

30. Byun JM, Yoon SS, Koh Y, et al. Incorporating hematopoietic stem-cell transplantation after second-line carfilzomib-lenalidomide-dexamethasone (KRd). Ther Adv Hematol. 2020;11:2040620720921046.

31. Miguel JS, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14(11):1055-1066.
32. Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(6):781-794.
33. Dimopoulos MA, Terpos E, Boccadoro M, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(6):801-812.
34. Richardson PG, Perrot A, Miguel JS, et al. Isatuximab-pomalidomide-dexamethasone versus pomalidomide-dexamethasone in patients with relapsed and refractory multiple myeloma: final overall survival analysis. Haematologica. 2024 Feb 1. [Epub ahead of print]
35. Ball S, Behera TR, Anwer F, Chakraborty R. Risk of kidney toxicity with carfilzomib in multiple myeloma: a meta-analysis of randomized controlled trials. Ann Hematol. 2020;99(6):1265-1271.
36. Musto P, Anderson KC, Attal M, et al. Second primary malignancies in multiple myeloma: an overview and IMWG consensus. Ann Oncol. 2017;28(2):228-245.

Table legends

Table 1. Baseline patient demographic, disease, and treatment data

Abbreviations: n, number; ECOG PS, Eastern Cooperative Group Performance Status; ISS, International Staging System; R-ISS, revised international staging system; M protein, monoclonal protein; FISH, fluorescence in situ hybridization; ANC, Absolute neutrophil count; SCT, stem cell transplantation; KRd, carfilzomib, lenalidomide, and dexamethasone; N/A, not available.

*8 IgD, 2 IgE, and 14 non-secretory myeloma.

Eighteen double-hit patients with del(17p) and t(4;14) (12 patients), t(4;14) and t(14;16) (6 patients), and two triplet-hit patients with del(17p), t(4;14), and t(14;16) were included.

Table 2. Comparison of the effectiveness and efficacy of KRd treatment from current and phase III ASPIRE study

Abbreviations: n, number; MRD, minimal residual disease; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease; mo, months; RDI, relative dose intensity.

*Overall response rate = (number of patients who achieved PR)/(number of response-evaluable patients) × 100.

Table 3. Univariate and multivariate analysis of high-risk factors affecting progression-free and overall survival

Abbreviations: n, number; HR, hazard ratio; MM, multiple myeloma; ISS, international staging system; R-ISS, revised international staging system; KRd, carfilzomib, lenalidomide, and dexamethasone; M protein, monoclonal protein; CRAB, hypercalcemia, renal failure, anemia, or bone lesions.

Table 4. Adverse event profile of the carfilzomib, lenalidomide and dexamethasone combination chemotherapy in the real-world practice compared with ASPIRE study

Abbreviations, AEs, adverse event; SAE, severe adverse event; n, number. adverse events; n, number.

*Detailed information listed in Supplementary Table 4.

Table 5. Comparison of the baseline characteristics and the effectiveness or efficacy of the KRd studies.

Abbreviations: KRd, carfilzomib-lenalidomide-dexamethasone; Retro, retrospective; no., number; ECOG PS, Eastern cooperative group performance status; Prev., previous; EMD, extramedullary disease; M protein, monoclonal protein; CrCl, creatinine clearance; Len, lenalidomide; ASCT, autologous stem cell transplantation; ORR, overall response rate; VGPR, very good partial response; PFS, progression-free survival; OS, overall survival; mo, months; N/A, not available; NR, not reached.

* Trial ineligibility is summarized in Supplementary Figure 1.

Tables

Table 1. Baseline patient demographic, disease, and treatment data

	Current	ASPIRE
Study design	Retrospective	Phase III
Patient number, n	364	396
Age, median years (range)	63 (28-85)	66 (38-91)
≥65 years, n (%)	149 (41)	192 (53)
≥75 years, n (%)	26 (7)	
Male gender, n (%)	205 (56)	207 (58)
ECOG PS, n (%)		
0 or 1	301 (84)	336/354 (95)
2	37 (10)	18/354 (5)
≥3	21 (6)	0
Unknown	5	
ISS, N (%)	At diagnosis	At study entry
I and II	215 (59)	315 (88)
III	127 (35)	45 (12)
Unknown	22 (6)	0
R-ISS, N (%)	At diagnosis	N/A
I and II	239 (66)	
III	76 (21)	
Unknown	49 (13)	
M-protein type		
IgG	201 (55)	
IgA	72 (20)	
IgM	1 (0.3)	
Light chain	64 (18)	
Other*	24 (7)	
Unknown	2 (1)	
Light chain type		
Kappa	192 (53)	
Lambda	154 (42)	
Negative	11 (3)	
Unknown	7 (2)	
Cytogenetic risk by FISH, n (%)		
High risk†	98 (27)	75 (21)
del(17p), n (%)	60 (16)	36 (10)
t(4;14), n (%)	46 (13)	36 (10)
t(14;16), n (%)	14 (4)	N/A
Standard risk	182 (50)	199 (55)
Unknown	84 (23)	86 (24)
ANC, /µL, median (range)	2,500 (322-17,500)	
< 1,000/µL, n (%)	16 (4)	0

Platelet, $x10^3$/µL, median (range)	158 (16-454)	
< 50 $x10^3$/µL, n (%)	23 (6)	0
Creatinine clearance, median, mL/min (range)	76.37 (5.98-364.90)	
≥60 mL/min, n (%)	233 (64)	281 (78)
30-<60 mL/min, n (%)	77 (21)	74 (21)
<30 mL/min, n (%)	36 (10)	5 (1)
Unknown	18 (5)	
Extramedullary plasmacytoma	88 (24)	N/A (at any time)
Paraskeletal	55 (15)	
Soft tissue	32 (9)	
Not specified	1 (0.3)	
Number of prior regimens, median (range)	1 (1-4)	
1 prior regimen, n (%)	311 (85)	224 (62)
2 prior regimens, n (%)	41 (11)	136 (38)
3 prior regimens, n (%)	10 (3)	
4 prior regimens, n (%)	2 (1)	
Prior therapies, n (%)		
Bortezomib	326 (90)	248 (69)
Thalidomide	239 (66)	157 (44)
Lenalidomide	1 (0.3)	44 (12)
Autologous SCT	201 (55)	212 (59)
Allogeneic SCT	4 (1)	
Refractory to bortezomib	120 (33)	4 (1)
Refractory to thalidomide	92 (25)	
Time from diagnosis to KRd treatment, median, months (range)	25.0 (1.1-183.8)	44.2 (3-281)

Abbreviations: n, number; ECOG PS, Eastern Cooperative Group Performance Status; ISS, International Staging System; R-ISS, revised international staging system; M protein, monoclonal protein; FISH, fluorescence in situ hybridization; ANC, Absolute neutrophil count; SCT, stem cell transplantation; KRd, carfilzomib, lenalidomide, and dexamethasone; N/A, not available.

*8 IgD, 2 IgE, and 14 non-secretory myeloma.

Eighteen double-hit patients with del(17p) and t(4;14) (12 patients), t(4;14) and t(14;16) (6 patients), and two triplet-hit patients with del(17p), t(4;14), and t(14;16) were included.

Table 2. Comparison of the effectiveness and efficacy of KRd treatment from current and phase III ASPIRE study

	Current	ASPIRE phase III
Patient number, n	364	396
Response evaluable patients, n (%)	354 (97)	
Flow MRD-negative	22 (6)	
sCR	23 (6)	9 (2)
CR	113 (31)	42 (12)
VGPR	88 (24)	131 (36)
PR	71 (20)	240 (67)
MR	3 (1)	N/A
SD	15 (4)	40 (11)
PD	19 (5)	
Not evaluable	10 (3)	
Overall response rate*, ≥PR, N (%) (n=354)	317 (90)	282 (78)
Treatment cycles, median (range)	13 (1-55)	17 (1-34)
Time to response, mo, median (range)	1.9 (0.1-39.6)	1.1
Time to best response, mo, median (range)	3.9 (0.3-39.6)	N/A
Carfilzomib RDI, median (range)	1.00 (0.05-1.00)	
Lenalidomide RDI, median (range)	0.81 (0.01-1.00)	
Dexamethasone RDI, median (range)	0.79 (0.06-1.00)	

Abbreviations: n, number; MRD, minimal residual disease; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease; mo, months; RDI, relative dose intensity.

*Overall response rate = (number of patients who achieved PR)/(number of response-evaluable patients) × 100.

Table 3. Univariate and multivariate analysis of high-risk factors affecting progression-free and overall survival

		Progression free survival							Overall survival						
					Univariate analysis		Multivariate analysis					Univariate analysis		Multivariate analysis	
		n	Event	Median PFS (months)	HR (95% CI)	P value	HR (95% CI)	P value	n	Event	Median OS (months)	HR (95% CI)	P value	HR (95% CI)	P value
At MM diagnosis															
ISS	I, II	215	154	26.1					215	72	-				
	III	127	93	18.7	1.194 (0.923-1.545)	0.1771			127	59	41.6	1.628 (1.154-2.299)	0.0056		
R-ISS	I, II	239	169	26.1					239	77	-				
	III	76	57	18.7	1.484 (1.099-2.005)	0.0101			76	42	26.5	2.323 (1.593-3.389)	<0.0001		
Cytogenetic risk	Standard	182	116	28.5					182	57	-				
	High	98	79	11.4	1.848 (1.387-2.463)	<0.0001	2.267 (1.313-3.914)	0.0033	98	47	39	1.942 (1.319-2.859)	0.0008	2.383 (1.258 to 4.515)	0.0077
At the time of KRd treatment															
Extramedullary disease	No	24	15	38.9					24	6	-				
	Yes	87	70	13.6	2.124 (1.205-3.745)	0.0092	3.641 (1.636-8.102)	0.0015	87	46	35.5	2.547 (1.084-5.983)	0.0319	2.750 (1.018 to 7.431)	0.0461
Doubling of M protein within 2-3 months	No	291	208	25.4					291	106	59.5				
	Yes	43	34	13.9	1.453 (1.010-2.089)	0.0440	2.992 (1.401-6.390)	0.0046	43	23	37.8	1.807 (1.151-2.839)	0.0102	2.440 (1.114 to 5.344)	0.0257
Symptomatic MM	No	98	65	32.2					98	23	59.5				
	Yes	266	200	18.9	1.500 (1.133-1.986)	0.0046			266	116	51.2	2.213 (1.414-3.464)	0.0005		
Amyloidosis	No	357	260	35.3					357	136	-				
	Yes	7	5	23.4	0.707 (0.292-1.713)	0.4423			7	3	59.5	0.930 (0.296-2.919)	0.9006		
Plasma cell leukemia	No	300	214	23.1					300	114	59.5				
	Yes	3	3	4.8	3.058 (0.974-9.599)	0.0554			3	3	6.9	6.670 (1.846-16.871)	0.0073		

Abbreviations: n, number; HR, hazard ratio; MM, multiple myeloma; ISS, international staging system; R-ISS, revised international staging system; KRd,

carfilzomib, lenalidomide, and dexamethasone; M protein, monoclonal protein; CRAB, hypercalcemia, renal failure, anemia, or bone lesions.

Table 4. Adverse event profile of the carfilzomib, lenalidomide and dexamethasone combination chemotherapy in the real-world practice compared with ASPIRE study

	Present study (n=364)		ASPIRE study (n=396)	
Median follow-up, mo	35		67	
Any AEs, n (%)	317 (87)		57 (100)	
Any grade ≥3 AEs, n (%)	203 (56)		84%	
Any SAEs, n (%)			19 (33)	
AE resulting in dose reduction, n (%)			12 (21)	
Carfilzomib	98 (27)		7 (2)	
Lenalidomide	137 (38)		7 (12)	
Dexamethasone	141 (39)		5 (9)	
AE resulting in discontinuation of any drug, n (%)			8 (14)	
Carfilzomib	44 (12)			
Lenalidomide	44 (12)			
Dexamethasone	46 (13)			
AE resulting discontinuation of KRd therapy, n (%)	31 (9)		60 (15)	
Death due to AE, n (%)	6 (2)		6 (2)	
	All grades	Grade ≥ 3 AEs	All grades	Grade ≥ 3 AEs
Adverse events of interest, n (%)				
Dyspnea	54 (15)	14 (4)	76 (19)	11 (3)
Hypertension	12 (3)	2 (1)	56 (14)	17 (4)
Cardiac failure	11 (3)	5 (1)	25 (6)	15 (4)
Ischemic heart disease	3 (1)	1 (0)	23 (6)	13 (3)
Acute kidney injury	35 (10)	6 (2)	33 (8)	13 (3)
Arrhythmias	6 (2)	3 (1)		
Deep vein thrombosis	12 (3)	2 (1)	23 (7)	7 (2)
New primary malignancy	8 (2)			
Treatment stop due to AEs*	31 (9)		60 (15)	
Death due to AEs	6 (2)		6 (2)	

Abbreviations, AEs, adverse event; SAE, severe adverse event; n, number. adverse events; n, number.

*Detailed information listed in Supplementary Table 4.

Table 5. Comparison of the baseline characteristics and the effectiveness or efficacy of the KRd studies.

	Current	Korea[14]	Tuscan[20]	Italy[21]	Europe Israel[22]	Japan[23]	ASPIRE[1]
Study design	Retro	Retro	Prospective observational	Retro	Prospective observational	Prospective observational	phase III
Patient no.	364	55	85	600	383	31	396
Age > 65 years	37%	36%	N/A (>=75 years 6%)	48%	N/A (median 65)	N/A (median 67)	47%
ECOG PS ≥3	6%	9%		N/A	N/A (ECOG PS 2-4, 15%)	6%	0
Trial-ineligibility	59%	N/A	N/A	N/A	N/A (Frail 28%)	N/A	0%
Prev. lines of therapy, median (range)	1 (1-4)	2 (1-5)	1-2	2 (1-11)	1 (1-2)	1 (1-4)	2 (1-3)
High-risk cytogenetics	27%	31%	26%	25%	15%	23%	12%
EMD	24%	N/A	4%	N/A	N/A	N/A	N/A
Doubling of M protein within 2-3 months	12%	N/A	N/A	N/A	N/A	N/A	N/A
CrCl <30 mL/min	10%	9%	7%	8%	N/A	N/A (3%, Cr ≥2mg/dL)	0
Len-refractory	0.3%	25%	6%	14%	57%	32%	0
Prior ASCT	55%	55%	60%	45%	64%	N/A	56%
ORR (≥VGPR)	90% (69%)	73% (35%)	95% (57%)	73% (54%)	84% (67%)	81% (52%)	87% (70%)
Median follow-up duration (mo)	35	14	40	16	18	28	67
Median PFS (mo)	23	9	36	22	N/A	2-year 59%	26
Median OS (mo)	60	22	5-year 73%	35	N/A	2-year 80%	48

Abbreviations: KRd, carfilzomib-lenalidomide-dexamethasone; Retro, retrospective; no., number; ECOG PS, Eastern cooperative group performance status; Prev., previous; EMD, extramedullary disease; M protein, monoclonal protein; CrCl, creatinine clearance; Len, lenalidomide; ASCT, autologous stem cell transplantation; ORR, overall response rate; VGPR, very good partial response; PFS, progression-free survival; OS, overall survival; mo, months; N/A, not available; NR, not reached.
* Trial ineligibility is summarized in Supplementary Figure 1.

Figure legends

Figure 1. Survival analysis in the total cohort. (A) Progression-free survival, and (B) overall survival.

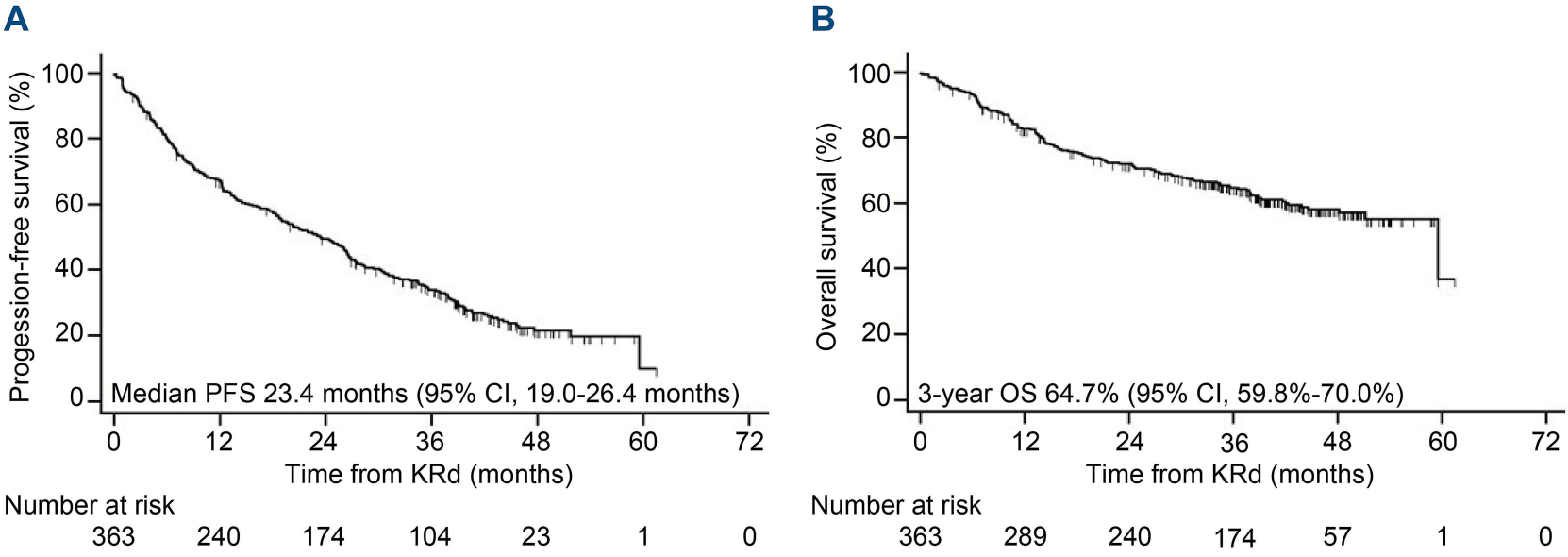
Figure 2. Survival analysis according to the post-KRd transplantation.

(A) Progression-free survival; no vs. yes = 22.4 months (95% CI, 18.0-26.1) vs. 37.0 months (95% CI, 22.0-38.9) (P=0.0259). (B) 3-year OS rate; no vs. yes = 62.2% (95% CI, 57.1-67.8%) vs. 100% (95% CI, 100.0-100.0%), P=0.0005. Survival analysis according to the salvage chemotherapy in post-KRd relapse. (C) Progression-free survival2, pom-based vs. newer target vs. conventional = 23.3 months (15.9-54.3) vs. 32.5 months (95% CI, 14.9-59.6), vs. 19.8 months (95% CI, 12.9-54.4), respectively, P=0.2088. (D) 3-year OS rate = pom-based vs. newer target vs. conventional = 57.3% (95% CI, 49.3-66.7%) vs. 70.2% (95% CI, 51.0-96.7%) vs. 51.1% (95% CI, 37.5-69.7%), respectively, P=0.2460.

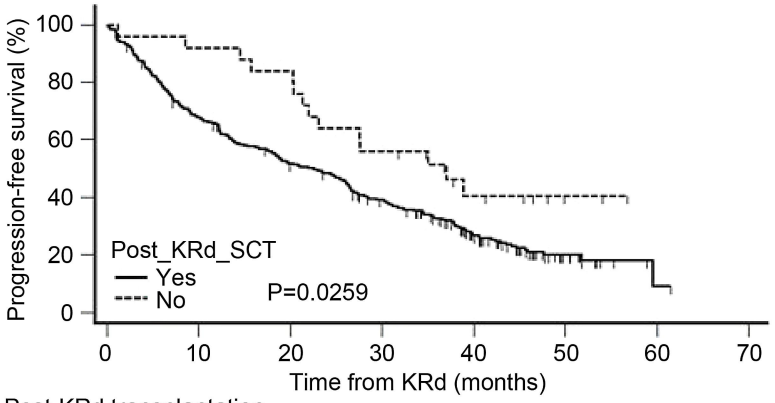
*Definition of progression-free survival2 = Time from the start of KRd therapy to the date of progression after post-KRd salvage chemotherapy

**Category of salvage chemotherapy: conventional, alkylator-, thalidomide-, bortezomib- and ixazomib-based regimen; pom-based, pomalidomide/dexamethasone, pomalidomide/cyclophosphamide/dexamethasone, and carfilzomib/pomalidomide/dexamethasone; and newer target agents, daratumumab-, belantamab-, teclistamab-, elranatamab-, and venetoclax-based chemotherapy.

Abbreviations: KRd, carfilzomib, lenalidomide, and dexamethasone; SCT, stem cell transplantation; CI, confidence interval; pom, pomalidomide.


A
Progression-free survival (%)
100
80
60
40
20
0
Median PFS 23.4 months (95% CI, 19.0-26.4 months)
0
12
24
36
48
60
72
Time from KRd (months)
Number at risk
363
240
174
104
23
1
0
B
Overall survival (%)
100
80
60
40
20
0
3-year OS 64.7% (95% CI, 59.8%-70.0%)
0
12
24
36
48
60
72
Time from KRd (months)
Number at risk
363
289
240
174
57
1
0

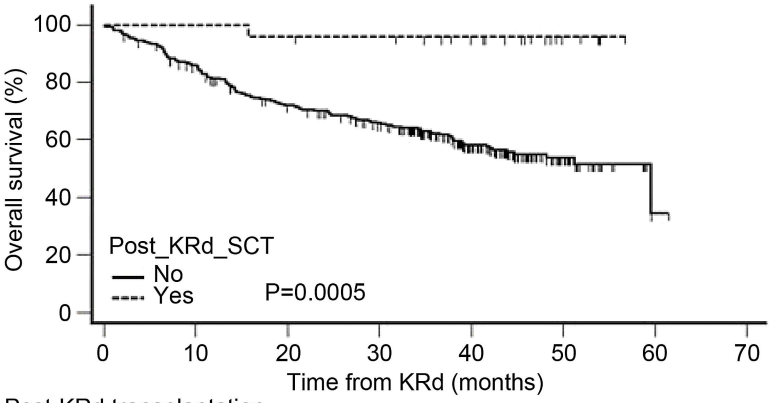
A



Post-KRd transplantation
Number at risk

Group: No							
338	228	170	123	57	14	1	0
Group: Yes							
25	23	21	14	7	2	0	0

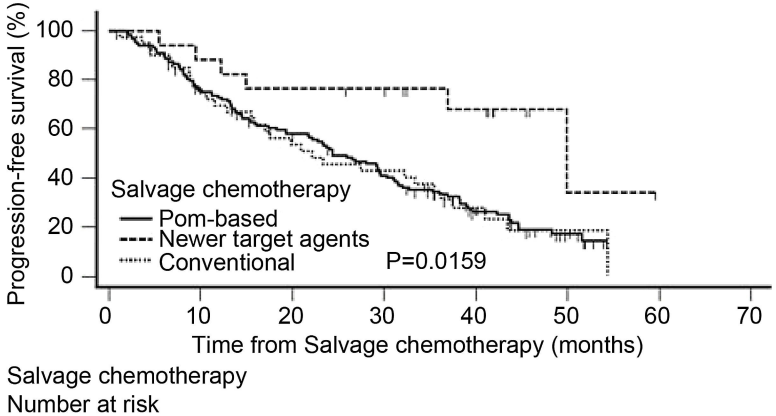
B



Post-KRd transplantation
Number at risk

Group: No							
338	284	227	195	110	34	1	0
Group: Yes							
25	25	24	23	18	5	0	0

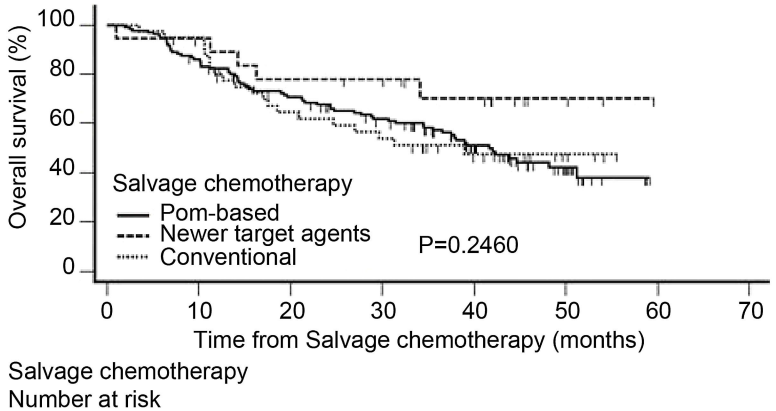
C



Salvage chemotherapy
Number at risk

Group: Pom-based							
135	99	73	50	23	7	0	0
Group: New target agents							
18	15	13	12	8	1	0	0
Group: Conventional							
40	29	20	16	7	3	0	0

D



Salvage chemotherapy
Number at risk

Group: Pom-based							
137	117	90	73	44	16	0	0
Group: Newer target agents							
19	17	14	13	9	3	0	0
Group: Conventional							
41	38	25	20	12	4	0	0

Supplements

Supplementary methods

Supplementary Table and Figure legends

Supplementary Table 1. Post-KRd treatment

*Pomalidomide/dexamethasone, pomalidomide/cyclophosphamide/dexamethasone, and carfilzomib/pomalidomide/dexamethasone

Cyclophosphamide/dexamethasone, melphalan/dexamethasone, bendamustine, dexamethasone/cyclophosphamide/etoposide/cisplatin

‡Daratumumab, daratumumab/bortezomib/dexamethasone, and daratumumab/pomalidomide/dexamethasone

§Velyx, bortezomib, and bortezomib/dexamethasone

¶Belantamab, belantamab/bortezomib/lenalidomide/dexamethasone, belanatamab/dostarimab, and belantamab/bortezomib/dexamethasone

‖Teclistamab/daratumumab/dexamethasone

**Elranatamab, elranatamab/daratumumab

Abbreviations: KRd, Carfilzomib, lenalidomide, and dexamethasone

Supplementary Table 2. Univariate and multivariate analyses of the patient characteristics affecting progression-free and overall survival

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Group Performance Status; HR, hazard ratio.

Supplementary Table 3. Univariate and multivariate analyses of previous treatments and responses affecting progression-free and overall survival

Abbreviations: CI, confidence interval; HR, hazard ratio; n, number; SCT, stem cell transplantation.

Supplementary Table 4. Cause of treatment cessation owing to adverse events

Abbreviations: AE, adverse event; n, number; SAE, severe adverse event.

Supplementary Table 5. Toxicity profile after KRd therapy

*Newly developed or aggravated peripheral neuropathy after administering carfilzomib, lenalidomide, and dexamethasone combination therapy.

Abbreviations: KRd, Carfilzomib, lenalidomide, and dexamethasone

Supplementary Figure 1. Characteristics of the trial-ineligible patients.
Abbreviations: ANC, Absolute neutrophil count; CCr, creatinine clearance; ECOG PS, Eastern cooperative group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; LOT, lines of therapy; PLT, platelet; PN, peripheral neuropathy.

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Abbreviations: ISS, International Staging System; M protein, monoclonal protein; R-ISS, Revised International Staging System; SCT, stem cell transplantation.

Supplementary Figure 3. Survival according to clinical trial eligibility
(A) Progression-free survival
(B) Overall survival.
[1]The Kaplan–Meier curve does not reach the probability of 0.5.

Supplementary Figure 4. Differences of baseline creatinine clearance according to acute kidney injury after KRd therapy.
Abbreviations: KRd, Carfilzomib, lenalidomide, and dexamethasone

Supplementary methods

This study included patients with RRMM whose disease was refractory, relapsed and refractory, or progressive after at least one line of therapy[1]. KRd was administered according to the ASPIRE study protocol[1]: carfilzomib was infused intravenously starting with 20 mg/m^2 on days 1 and 2 of cycle 1. This was increased to 27 mg/m^2 on days 1, 2, 8, 9, 15, and 16 until cycle 12, and on days 1, 2, 15, and 16 during cycles 13–18, after which carfilzomib was stopped. Lenalidomide was administered orally at a dose of 25 mg on days 1–21. Its dosage was adjusted according to renal impairment. Dexamethasone was administered at a dosage and schedule that was determined by the treating physician. Additionally, 62 patients were evaluated for minimal residual disease (MRD) by using the EuroFlow standard operative procedure. Responses were designated according to the IMWG response criteria as follows: MRD-negative complete response (CR), stringent complete response (sCR), CR, very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), and progressive disease (PD)[2]. Refractoriness to bortezomib or thalidomide was defined as a disease that did not achieve MR, progressed during treatment, or progressed within 60 days after the administration of bortezomib or thalidomide. Clinical trial-ineligibility was not meeting the eligibility criteria specified in ASPIRE trial: Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 3, ongoing heart disease, chronic or active hepatitis B virus (HBV), hepatitis C virus (HCV) infection, absolute neutrophil count (ANC) < 1,000/μL, hemoglobin < 8 g/dL, platelet count < 50,000/μL, calculated creatinine clearance (CCr) < 50 mL/min, plasma cell leukemia, ongoing > grade 2 peripheral neuropathy, underlying cancer, > 3 prior lines of therapy, primary refractoriness to previous therapy, bortezomib-refractoriness, and lenalidomide-refractoriness. Symptomatic diseases were excluded from the trial-ineligibility criteria because recent clinical trials did not preclude the biochemical progression of the disease. AEs observed during KRd treatment were assessed using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03.

1. Anderson KC, Kyle RA, Rajkumar SV, et al. Clinically relevant end points and new drug approvals for myeloma. *Leukemia* 2008;22(2):231-9.

2. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.

Supplementary Tables

Supplementary Table 1. Post-KRd treatment

	n (%)
Consolidative transplantation	25 (6.9)
Autologous SCT	21 (5.8)
Allogeneic SCT	4 (1.1)
Salvage chemotherapy	197 (54.1)
Pomalidomide-based combination therapy*	137 (37.6)
Alkylator-based†	18 (4.9)
Daratumumab-based combination therapy‡	14 (3.8)
Thalidomide/cyclophosphamide/dexamethasone	10 (2.7)
Bortezomib-based combination therapy§	8 (2.2)
Belantamab-combination therapy¶	5 (1.4)
Teclistamab-combination therapy‖	4 (1.1)
Ixazomib/lenalidomide/dexamethasone	3 (0.8)
Elranatamab-combination therapy**	2 (0.5)
Venetoclax/dexamethasone	1 (0.3)

*Pomalidomide/dexamethasone, pomalidomide/cyclophosphamide/dexamethasone, and carfilzomib/pomalidomide/dexamethasone

†Cyclophosphamide/dexamethasone, melphalan/dexamethasone, bendamustine, dexamethasone/cyclophosphamide/etoposide/cisplatin

‡Daratumumab, daratumumab/bortezomib/dexamethasone, and daratumumab/pomalidomide/dexamethasone

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‖Teclistamab/daratumumab/dexamethasone

**Elranatamab, elranatamab/daratumumab

Abbreviations: KRd, Carfilzomib, lenalidomide, and dexamethasone

Supplementary Table 2. Univariate and multivariate analysis of patient characteristics affecting progression-free and overall survival

				Progression free survival						Overall survival			
				Univariate analysis		Multivariate analysis				Univariate analysis		Multivariate analysis	
		n	Event	HR (95% CI)	P value	HR (95% CI)	P value	n	Event	HR (95% CI)	P value	HR (95% CI)	P value
Patient characteristics													
Age	< 65	215	156					215	71				
	≥ 65	149	109	1.043 (0.816-1.333)	0.7343			149	68	1.496 (1.072-2.087)	0.0178	1.480 (1.050-2.086)	0.0253
ECOG PS	0-2	338	243					338	125				
	≥ 3	21	17	1.494 (0.913-2.445)	0.1102			21	11	1.725 (0.930-3.199)	0.0835		
Platelet	≥ 50,000/μL	330	235					330	116				
	< 50,000/μL	23	22	5.443 (3.442-8.610)	<0.0001	5.443 (3.442-8.610)	<0.0001	23	20	7.251 (4.410-11.920)	<0.0001	7.442 (4.517-12.261)	<0.0001
ANC	≥ 1,000/μL	336	242					336	128				

	< 1,000/μL	16	14	1.882 (1.095-3.233)	0.0221			16	8	1.624 (0.795-3.320)	0.1834		
Hemoglobin	≥ 8 g/dL	345	251					345	131				
	< 8 g/dL	8	6	1.398 (0.621-3.146)	0.4180			8	5	2.211 (0.904-5.407)	0.082		
Underlying liver disease	No	349	252					349	136				
	Yes	15	13	1.470 (0.841-2.570)	0.176			15	3	0.586 (0.187-1.841)	0.3601		
Underlying heart disease	No	345	250					345	130				
	Yes	19	15	1.276 (0.757-2.151)	0.3598			19	9	1.648 (0.838-3.240)	0.1479		
Underlying cancer	No	354	257					354	132				
	Yes	10	8	1.081 (0.535-2.185)	0.8286			10	7	1.804 (0.843-3.860)	0.1283		
Creatinine clearance	≥ 50 mL/min	262	184					262	89				
	< 50 mL/min	84	67	1.230 (0.928-	0.1497			84	42	1.571 (1.087-	0.0162		

				1.630)						2.272)			

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Group Performance Status; HR, hazard ratio.

Supplementary Table 3. Univariate and multivariate analysis of previous treatment and response affecting progression-free and overall survival

		Progression free survival						Overall survival					
				Univariate analysis		Multivariate analysis				Univariate analysis		Multivariate analysis	
		n	Event	HR (95% CI)	P value	HR (95% CI)	P value	n	Event	HR (95% CI)	P value	HR (95% CI)	P value
Previous therapy													
Autologous SCT	No	163	123					163	78				
	Yes	201	142	0.769 (0.604-0.979)	0.0331			201	61	0.518 (0.370-0.725)	0.0001		
Prior bortezomib	No	38	20					38	8				
	Yes	326	245	2.514 (1.573-4.018)	0.0001			326	131	2.696 (1.310-5.549)	0.0071		
Prior thalidomide	No	125	88					125	57				
	Yes	239	177	1.088 (0.842-1.406)	0.5176			239	82	0.694 (0.495-0.974)	0.0346		
Bortezomib refractory	No	205	151					205	78				
	Yes	120	94	1.294 (1.000-	0.0501			120	53	1.382 (0.974-	0.0699		

				1.676)						1.961)			
Bortezomib response duration	< 12mo	128	105					128	62				
	≥ 12mo	156	108	0.619 (0.473-0.810)	0.0005	0.619 (0.473-0.810)	0.0005	156	49	0.499 (0.342-0.726)	0.0003	0.499 (0.342-0.726)	0.0003
Thalidomide refractory	No	147	106					147	46				
	Yes	92	71	1.365 (1.010-1.845)	0.0432			92	36	1.511 (0.975-2.344)	0.0650		
Thalidomide response	< 12mo	87	71					87	36				
	≥ 12mo	119	81	0.534 (0.387-0.736)	0.0001			119	30	0.438 (0.268-0.716)	0.0010		

Abbreviations: CI, confidence interval; HR, hazard ratio; n, number; SCT, stem cell transplantation.

Supplementary Table 4. Cause of treatment cessation due to adverse events

Non-fatal AEs	n
Secondary malignancy (colon cancer, esophageal cancer, pancreatic cancer, and myelodysplastic syndrome)	4
Fatigue	4
Bone pain	2
Acute pulmonary thromboembolism	2
Congestive heart failure	2
Ischemic heart disease	1
Cerebrovascular disease	1
Septic shock	1
Pneumonia	2
COVID-19 infection	1
Foot gangrene due to cholesterol embolism	1
Cellulitis	1
Rhabomyolysis	1
Pancytopenia	1
Liver function abnormality	1
Fatal AEs	
Pneumonia	2
Ventricullar fibrillation associated with congestive heart failure	1
Lung cancer	1
Leukemia	2

Abbreviations: AE, adverse event; n, number; SAE, severe adverse event.

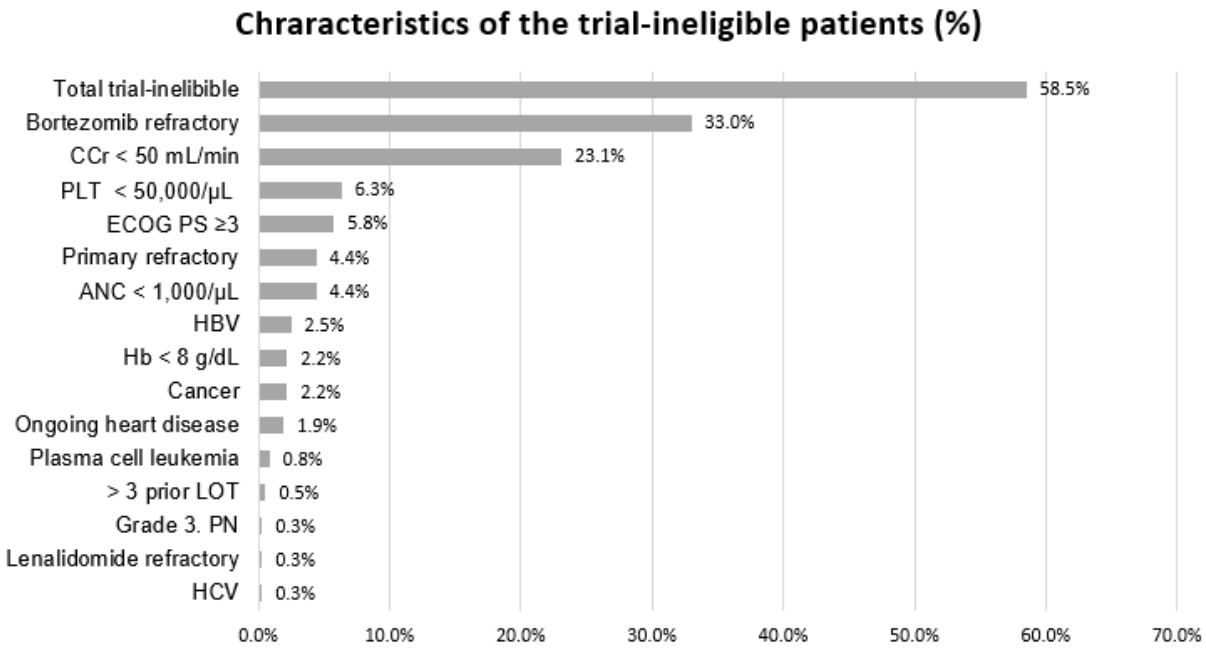
Supplementary Table 5. Toxicity profile after KRd therapy

	All grades	Grade ≥ 3 AEs	All grades	Grade ≥ 3 AEs
Hematologic adverse events, n (%)				
Anemia	138 (38)	60 (16)	167 (43)	70 (18)
Thrombocytopenia	155 (43)	73 (20)	114 (29)	65 (17)
Neutropenia	171 (47)	123 (34)	148 (38)	116 (30)
Neutropenic fever	17 (5)	11 (3)		
Non-hematologic adverse events, n (%)				
Fatigue	119 (33)	34 (9)	129 (33)	30 (8)
Hypokalemia	10 (3)	2 (1)	108 (28)	37 (9)
Cough	32 (9)	2 (1)	113 (29)	1 (0.3)
Pyrexia	24 (7)	5 (1)	112 (29)	7 (2)
Upper respiratory tract infection	63 (17)	3 (1)	112 (29)	7 (2)
Muscle spasm	32 (9)	4 (1)	104 (27)	4 (1)
Back pain	68 (19)	17 (5)		
Liver function test abnormalities	50 (14)	16 (4)		
Diarrhea	44 (12)	8 (2)		
Peripheral neuropathy*	31 (9)	9 (2)	67 (17)	10 (3)
Abdominal discomfort	36 (10)	2 (1)		
Dyspepsia	34 (9)	2 (1)		
Nausea	31 (9)	0		
Vomiting	17 (5)	2 (1)		
Constipation	50 (14)	1 (0.3)		
Rash	53 (15)	12 (3)		
Itching	42 (12)	12 (3)		
Headache	28 (8)	1 (0.3)		
Peripheral edema	29 (8)	4 (1)		
Insomnia	38 (10)	0		
Encephalopathy	2 (1)	2 (1)		
Interstitial lung disease	3 (1)	1 (0.3)		
Infection	77 (21)	42 (12)		

*Newly developed or aggravated peripheral neuropathy after administering carfilzomib, lenalidomide, and dexamethasone combination therapy.

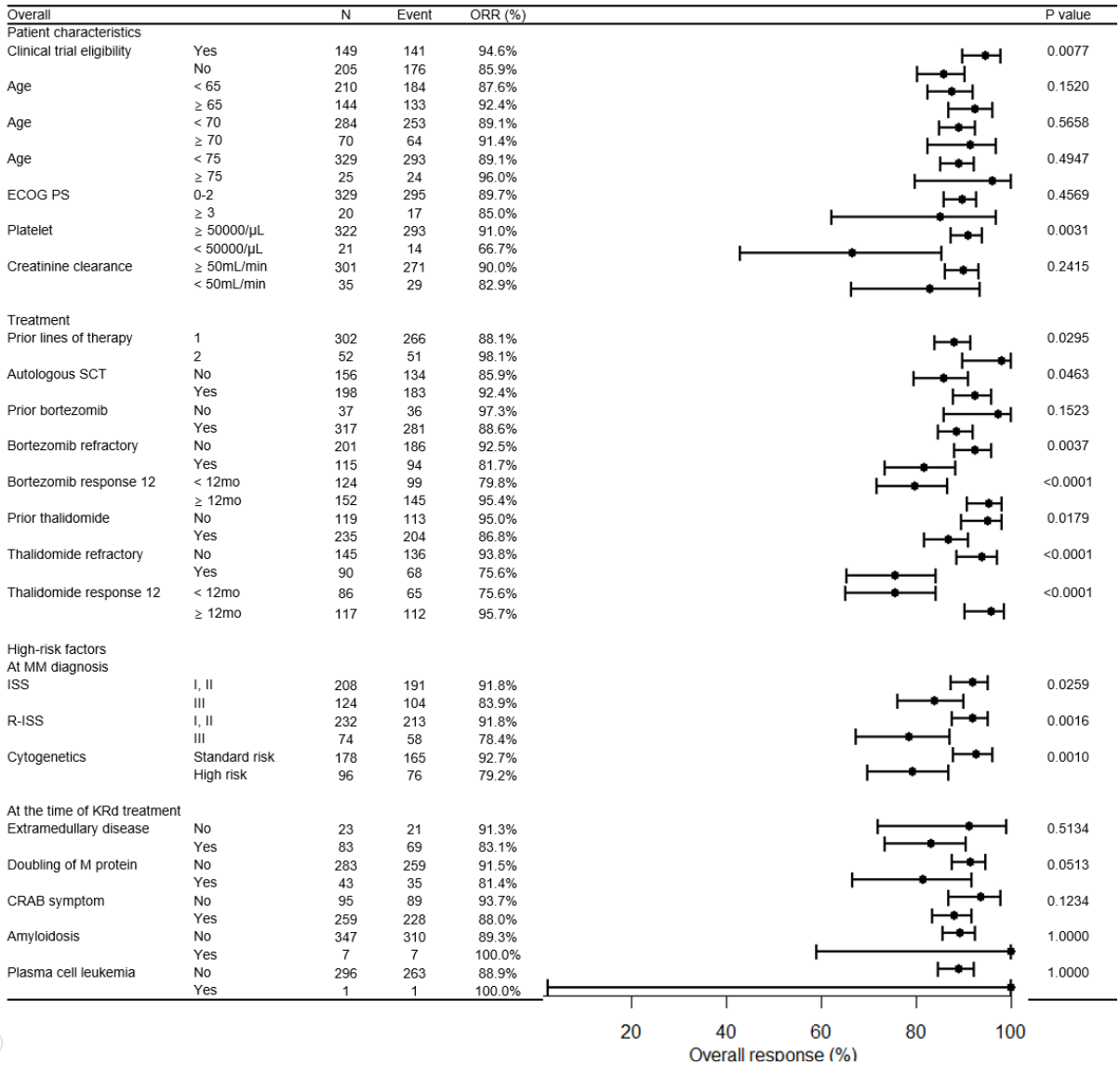
Abbreviations: KRd, Carfilzomib, lenalidomide, and dexamethasone

Supplementary Figure 1. Characteristics of the trial-ineligible patients.



Abbreviations: ANC, Absolute neutrophil count; CCr, creatinine clearance; ECOG PS, Eastern cooperative group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; LOT, lines of therapy; PLT, platelet; PN, peripheral neuropathy.

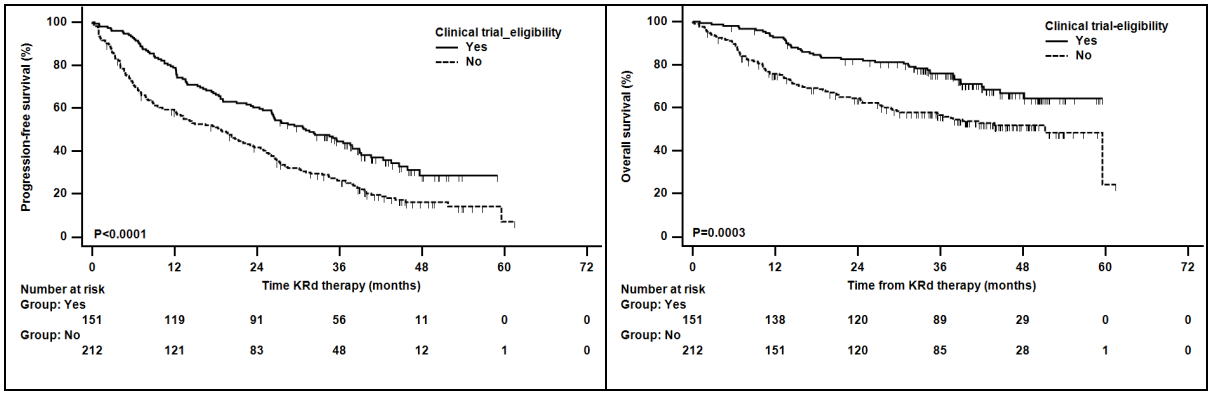
Supplementary Figure 2. Overall response rated according to patient, treatment, and disease related factors.



Abbreviations: ISS, International Staging System; M protein, monoclonal protein; R-ISS, Revised International Staging System; SCT, stem cell transplantation.

Supplementary Figure 3. Survival according to clinical trial eligibility

(A) Progression-free survival (B) Overall survival.



Progression-free survival

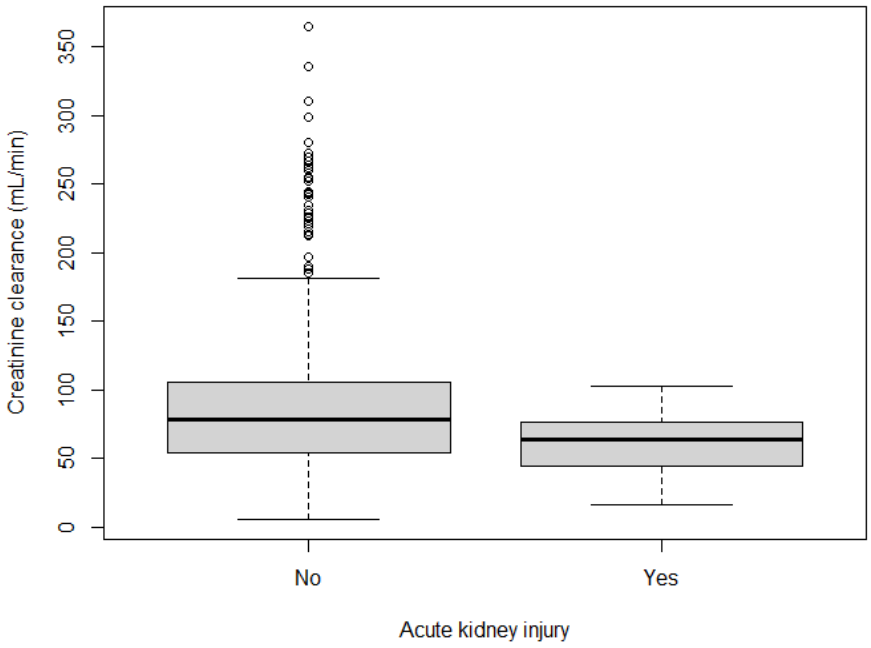
	overall	Clinical trial-eligibility	
		yes	no
median	23.4 months (95% CI, 19.0-26.4 months)	31.1 months (95% CI, 26.1-37.8 months)	18.7 months (95% CI, 12.4-22.6 months)
3-year	33.9% (95% CI, 29.3%-39.2%)	44.4% (95% CI, 37.1%-53.2%)	26.2% (95% CI, 20.7%-33.0%)

Overall survival

	overall	Clinical trial-eligibility	
		yes	no
Median	59.5 months (95% CI, 51.2-59.5 months)	-[1]	51.2 months (95% CI, 35.5-59.5 months)
3-year	64.7% (95% CI, 59.8%-70.0%)	75.9% (95% CI, 69.2%-83.2%)	56.5% (95% CI, 49.9%-63.9%)

[1] The Kaplan-Meier curve does not reach at probability of 0.5.

Supplementary Figure 4. Differences of baseline creatinine clearance according to acute kidney injury after KRd therapy.



Abbreviations: KRd, Carfilzomib, lenalidomide, and dexamethasone