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# Daratumumab, bortezomib, lenalidomide, and dexamethasone for transplant-eligible elderly patients with newly diagnosed multiple myeloma (KMM2101 trial)

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# Abstract

Evidence supporting daratumumab, bortezomib, lenalidomide, and dexamethasone (D-VRd) in transplant-eligible patients aged 65–69 years with newly diagnosed multiple myeloma (NDMM) remains limited, particularly among Asian patients. Furthermore, the efficacy of six cycles of D-VRd induction before autologous stem cell transplantation (ASCT) has not been prospectively evaluated. In this multicenter, single-arm, phase II study, 26 transplant-eligible patients aged 65–69 years with NDMM received six cycles of D-VRd induction followed by ASCT. Maintenance therapy consisted of daratumumab plus lenalidomide for 12 months, followed by daratumumab monotherapy for another 12 months. The primary endpoint was the rate of very good partial response (VGPR) or better after ASCT. All patients completed induction, and 25 (96.2%) underwent ASCT. The VGPR or better rate after ASCT was 96.2%. The MRD-negative rate was 92.3%, and 65.4% achieved sustained MRD negativity for 12 months. After a median follow-up of 42.5 months, 3-year progression-free and overall survival rates were 76.9% and 88.5%, respectively. Grade ≥ 3 neutropenia was the most common adverse event, while dose intensity was generally maintained. Six cycles of D-VRd induction followed by ASCT and fixed-duration daratumumab-based maintenance achieved deep and durable responses with manageable toxicity in fit, transplant-eligible patients aged 65–69 years.


# INTRODUCTION

Multiple myeloma (MM) is a malignant proliferation of plasma cells, which accounts for 10%-15% of all hematologic malignancy, making it the second most common hematologic malignancy worldwide (1). MM is most frequently diagnosed among people aged 65 to 74, with the median age being 69 years. This age group represents a clinically important population in treatment of MM because it includes both transplant-eligible and transplant-ineligible patients. Determining transplant eligibility in this population requires a comprehensive assessment of multiple patient- and disease-related factors. Although age remains one of the most important considerations(2), chronological age alone should not determine treatment eligibility. Instead, the decision should be individualized based on overall fitness, including comorbidities, organ function, functional status, and disease characteristics such as cytogenetic risk (3, 4).

Over the past several decades, survival outcomes in patients with MM have improved substantially, owing in part to the introduction of novel therapeutic agents together with advances in supportive care (5). Among these advances, the incorporation of anti-CD38 monoclonal antibodies into treatment regimens across multiple lines of therapy has further improved clinical outcomes, particularly in the frontline setting. For transplant-eligible patients, anti-CD38 monoclonal antibody-based quadruplet induction therapy has become the standard of care based on its demonstrated improvements outcomes and acceptable safety profiles (6–8). For example, in the phase 3 PERSEUS trial, the addition of daratumumab to bortezomib, lenalidomide, and dexamethasone (D-VRd) as induction and consolidation therapy, followed by daratumumab-lenalidomide maintenance, significantly reduced the risk of disease progression or death by 58% compared with the standard VRd-based approach (hazard ratio [HR], 0.42;

95% confidence interval [CI], 0.30–0.59; $p < 0.001$) (7). D-VRd also significantly increased the rate of minimal residual disease (MRD) negativity at the $10^{-5}$ sensitivity threshold (75.2% vs. 47.5%; $p < 0.001$). The incidence of treatment-emergent adverse events (AEs) leading to treatment discontinuation was lower in the D-VRd group (8.8%) than in the VRd group (21.3%).

However, because a subset of patients aged ≥ 65 years may not be candidates for autologous stem cell transplantation, evidence regarding D-VRd in this population has been derived primarily from subgroup analyses (9). Furthermore, because most studies have used four cycles of D-VRd induction before ASCT followed by two cycles of D-VRd consolidation, the role of six cycles of D-VRd induction before ASCT has not yet been evaluated. Asian patients were also underrepresented in these studies, limiting the generalizability of their findings.

Therefore, we conducted a phase II study to better define the efficacy and safety of 6 cycles of D-VRd in this less well-validated population.

## PATIENTS and METHODS

# Trial design and Patients

In this single-arm, open label, multicenter, phase II study, patients aged 65–69 years with newly diagnosed multiple myeloma (NDMM), who were deemed transplant-eligible were included. Other key inclusion criteria were as follows: at least one measurable disease according to the International Myeloma Working Group (IMWG) criteria, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate hepatic, renal, and bone marrow functions to undergo ASCT. Patients with significant cardiac dysfunction, such as myocardial infarction, unstable angina, New York Heart Association (NYHA) class III-IV congestive heart failure within 6 months, or uncontrolled arrhythmia, were excluded. Other key exclusion criteria included prior therapy for MM, active uncontrolled infection, and plasma cell disorders other than MM (i.e. light chain amyloidosis, plasma cell leukemia, or Waldenstroem Macroglobulinemia). Detailed eligibility criteria are provided in the Supplementary Materials.

Patients received six cycles of D-VRd induction consisting of daratumumab (8 mg/kg intravenously, Cycle 1 D1-D2; 16 mg/kg intravenously; weekly through cycles 1 and 4; every three week through cycles 5 and 6), bortezomib (1.3 mg/m² subcutaneously on days 1, 4, 8 and 11), lenalidomide (25 mg once daily on days 1–14), and dexamethasone (20 mg once daily on days 1, 2, 8, 9, 15, and 16) administered every 3 weeks. Hematopoietic stem cells were collected after the first 3 or 4 cycles of induction therapy according to institutional policy using granulocyte colony-stimulating factor (G-CSF), with or without plerixafor. Patients received high-dose melphalan (200 mg/m²) as conditioning chemotherapy over 24 to 48 hours, followed by ASCT, which was to be performed within 6 weeks after completion of the six cycles of induction treatment. Maintenance therapy was initiated within 100 days after stem cell infusion (day 0). During the first 12 months, patients received daratumumab (16 mg/kg every 4 weeks) plus

lenalidomide (10 mg once daily on days 1–21 of each 28-day cycle) (maintenance I phase). During the subsequent 12 months, daratumumab monotherapy (16 mg/kg every 8 weeks) was administered (maintenance II phase) (Supplementary Fig. 1).

Dose reduction of daratumumab was not permitted throughout the study. In the event of recurrent grade 3 or any grade 4 infusion-related reaction, daratumumab was permanently discontinued. Dose modification guidelines for bortezomib, lenalidomide, and dexamethasone are provided in the Supplementary Materials. Antiviral prophylaxis was required during bortezomib and/or daratumumab treatment. Aspirin at a standard prophylactic dose (100 mg once daily) was mandated for thromboprophylaxis. Pneumocystis jirovecii pneumonia prophylaxis and proton pump inhibitors were recommended according to institutional guidelines during dexamethasone treatment. The use of bisphosphonate was permitted.

The study was an investigator-initiated study led by the Korean Multiple Myeloma Working Party (KMM2101 study). All procedures and study drugs covered under the standard of care, including bortezomib during cycles 1–4 and dexamethasone throughout induction therapy, were covered by the Korean National Health Insurance Service. Johnson & Johnson Korea provided research funding for this study and supplied daratumumab and bortezomib administered during cycles 5–6. Samyang Biopharm supplied lenalidomide (Lenalid®) throughout the study. The sponsors had no role in patient enrollment, data collection, data analysis, data interpretation, manuscript preparation, or the decision to submit the manuscript for publication.

# Statistical Analysis

The primary endpoint of the study was very good partial response (VGPR) rates after ASCT. The secondary endpoints included overall response rate (ORR), complete response (CR) rate, minimal residual disease (MRD) negativity rate, duration of response (DoR), progression-free survival (PFS), and overall survival (OS). Response was assessed according to the IMWG response criteria(10), and the subgroup comparisons were performed using $\chi^2$ tests. MRD negativity was assessed in 60 days after stem cell infusion using next-generation flow cytometry (11) in patients who had achieved at least VGPR. Two subsequent assessments were performed after maintenance phase I and maintenance phase II, respectively. Twelve-month and 24-month sustained MRD negativity were defined as MRD negativity confirmed 12 and 24 months, respectively, after the first documented MRD-negative assessment. The MRD test was centrally and primarily performed using next-generation flow cytometry with a $10^{-5}$ sensitivity (11). DoR was calculated from the start date of CR, VGPR, or PR (whichever response is achieved first) and subsequently confirmed, until the date that progressive disease (PD) is objectively documented. PFS was defined as the time from written consent to disease progression or death from any cause, and OS as the time from consent to death from any cause. DoR, PFS, and OS were calculated using the Kaplan–Meier method. Subgroups comparison for survival was carried out using the log-rank test. High-risk cytogenetics were defined by the presence of del(17p), t(4;14), and/or t(14;16) as

identified by fluorescence in situ hybridization (FISH). Relative dose intensity (RDI) was calculated as the ratio of the delivered dose intensity to the planned dose intensity.

AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. For the primary endpoint, a one-sided p-value < 0.05 was considered to indicate that the prespecified criterion for success was met. For secondary endpoints, p-values are reported descriptively without a predefined significance threshold. All analyses were performed using IBM SPSS (version 29.0; IBM Corp., USA).

The sample size was determined using a one-sample Z-test for a proportion. Based on the results from GRIFFIN trial (6), an expected VGPR rate of 90.9% was set as the alternative hypothesis, against a null hypothesis proportion of 70.0%. With a one-sided alpha of 0.05 and 80% power, a sample size of 23 patients was required. Accounting for an anticipated 10% drop-out rate, a total of 26 patients were planned for enrollment. The total study duration was 54 months to ensure a minimum follow-up of 3 years for all patients.

## Ethical Considerations

All patients provided written informed consent before screening. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki or comparable ethical standards. An independent ethics committee or institutional review board approved the protocol at each site (SMC 2021-05-081; CNUHH-2022-123; CMC-2022-0329-0001; GNUH 2022-03-004; H-2202-040-1298; CUH 2022-02-022; CNUH 2022-02-077; 2022-05-030). This trial is was registered at the Clinical Research Information Service (CRIS), Republic of Korea (KCT0006549).

All authors declare no competing interest for this trial.

## RESULTS

# Patients’ characteristics

From January 2022 to February 2023, 26 consecutive patients were recruited from eight tertiary institutions in Korea. Twelve patients (46.2%) were male, and the median age of the patients was 67 years (range, 65–69). According to the International Staging System (ISS), 7 (26.9%), 14 (53.8%), and 5 (19.2%) patients were classified as stage I, II, and III, respectively. Based on the Revised International Staging System (R-ISS), 5 (19.2%), 17 (65.4%), and 4 (15.4%) patients were classified as stage I, II, and III, respectively. Nine patients (34.9%) had at least one high-risk cytogenetic abnormality by FISH. Detailed baseline characteristics provided in Table 1.

Table 1
Baseline characteristics

| **Age (median, range)** | **Patients (N, %)** |
|---|---|
| | **67 (65–69)** |
| Sex | |
| Male | 12 (46.2) |
| Female | 14 (53.8) |
| ECOG PS | |
| 0–1 | 25 (96.2) |
| 2 | 1 (5.8) |
| Heavy-chain subtype | |
| IgG | 16 (61.5) |
| IgA | 3 (11.5) |
| None | 7 (26.9) |
| Light-chain subtype | |
| Kappa | 12 (46.2) |
| Lambda | 13 (50.0) |
| None | 1 (3.8) |
| Anemia (hemoglobin < 10 g/dL) | 13 (50.0) |
| Estimated GFR < 40 mL/min | 1 (3.8) |
| BM PC% (median, range) | 70% (10–95) |
| Extramedullary disease | 4 (15.4) |
| ISS | |
| I | 7 (26.9) |
| II | 14 (53.8) |
| III | 5 (19.9) |
| R-ISS | |
| I | 5 (19.2) |
| II | 17 (65.4) |

* Three patients had two high-risk cytogenetic abnormalities

| Age (median, range) | Patients (N, %) |
|---|---|
| | **67 (65–69)** |
| III | 4 (15.4) |
| High-risk cytogenetics* | 9 (34.6) |
| t(4;14) | 6 (23.1) |
| t(14;16) | 2 (7.7) |
| del(17p) | 4 (15.4) |
| * Three patients had two high-risk cytogenetic abnormalities | |

# Treatment courses and efficacy

Response deepened throughout induction therapy, with VGPR rates increasing to 73.1% (19/26), 84.6% (22/26), and 92.3% (24/26) after cycles 4, 5, and 6, respectively. All patients completed induction treatment, and an ORR after cycle 6 was 100.0%, with 24 patients (92.3%) achieving VGPR and 2 (7.7%) achieving PR. The median time to response was 45 days (95% confidence interval (CI), 40.0–50.0). One patient who achieved VGPR after 6 cycles of induction treatment did not proceed to ASCT because of a decline in general condition. The patient has maintained an immunofixation-negative VGPR for more than 3 years and remains alive.

In the remaining 25 patients who proceeded to ASCT, 19 patients (76.0%) used plerixafor for stem cell collection. The median number of infused CD34 + stem cells was $2.9 \times 10^6$/kg (range, 0.7–6.8), and the median time to neutrophil engraftment was 12 days (range, 10–16). All of the 25 patients achieved at least VGPR, including stringent CR in 1 (3.8%), CR in 18 (69.2%), and VGPR in 6 patients (23.1%). Thus, the primary endpoint of the study was met. Of the 25 patients assessed for MRD status, 21 achieved MRD negativity at this point.

These patients subsequently entered maintenance I phase, and the 6 patients who had VGPR at the beginning of the phase achieved CR after the completion of maintenance treatment. Three patients discontinued treatment during this phase: two due to PD and one due to death from an unknown cause while remaining in CR. Two additional patients discontinued treatment after completing this phase: one due to PD and the other due to encephalopathy of unknown etiology, for which daratumumab-associated encephalopathy was suspected. Of the 22 patients assessed for MRD status, 20 patients achieved MRD negativity, including three who converted from MRD-positive after ASCT to MRD-negative.

The remaining 20 patients subsequently entered maintenance II phase, and all of them completed 6 cycles of treatment. During this phase, none of the patients stopped treatment due to PD or AEs. Of the 20 patients assessed for MRD status, 17 patients achieved MRD negativity. After completion of

maintenance II, 3 patients experienced PD after 4.6 months, 4.7 months, and 11.8 months, respectively. The treatment course and outcomes are depicted in Fig. 1. The overall MRD-negativity rate was 92.3% (24/26). The 12-month and 24-months sustained MRD-negativity rates were 65.4% (17/26), and 57.7% (15/26), respectively (Fig. 2).

With a median follow-up duration of 42.5 months (95% CI, 40.9–44.1), the estimated median PFS was not reached with the estimated 3-year and 4-year PFS rates being 76.9% (95% CI, 60.6% − 93.2%), and 71.0% (95% CI, 47.8% – 85.3%), respectively. The median OS was not reached, and the 3-year OS rate was 88.5% (95% CI, 68.2–96.2%) (Fig. 3). Overall, 5 deaths occurred, including 4 attributable to myeloma progression, and 1 unknown cause.

## Safety

Hematologic toxicity was the predominant AE, concentrated in the induction and maintenance periods and diminishing substantially thereafter. Neutropenia was the most common grade ≥ 3 hematologic toxicity, occurring in 10 of 26 patients (38.5%) during induction and in the same proportion, 10 of 26 patients (38.5%), during maintenance 1; during maintenance II, grade ≥ 3 neutropenia was no longer observed. Grade ≥ 3 thrombocytopenia followed a similar declining pattern, seen in 4 of 26 patients (15.4%) during induction, 1 of 26 (3.8%) during Maintain I, and none during maintenance II. Grade ≥ 3 anemia was uncommon and limited to the induction period (1 of 26, 3.8%).

Significant non-hematologic adverse events were rare throughout treatment. During induction, tumor lysis syndrome, grade ≥ 3 fatigue, and peripheral neuropathy each occurred in one patient (3.8%). During maintenance, isolated grade ≥ 3 events included rash (1 patient, 3.8%, in each of maintenance I and II), liver enzyme elevation (1 patient, 3.8%, during maintenance I), and pneumonia (1 patient, 3.8%, during maintenance I and II). Details are provided in Table 2.

Table 2
Summary of Treatment-emergent adverse events

| | | Induction | | Maintenance I | | Maintenance II | |
|---|---|---|---|---|---|---|---|
| | | Any grade | Grade ≥ 3 | Any grade | Grade ≥ 3 | Any grade | Grade ≥ 3 |
| **Hematologic** | Neutropenia | 13 (50.0%) | 10 (38.5%) | 12 (46.2%) | 10 (38.5%) | 1 (3.8%) | |
| | Thrombocytopenia | 13 (50.0%) | 4 (15.4%) | 6 (23.1%) | 1 (3.8%) | 3 (11.5%) | |
| | Anemia | 6 (23.1%) | 1 (3.8%) | 3 (11.5%) | | 1 (3.8%) | |
| **Infection** | COVID-19 | 1 (3.8%) | | 1 (3.8%) | | 2 (7.7%) | |
| | URI | 1 (3.8%) | | 5 (19.2%) | | | |
| | Pneumonia | 1 (3.8%) | | | 1 (3.8%) | 1 (3.8%) | 1 (3.8%) |
| | Febrile neutropenia | 1 (3.8%) | | | | | |
| **Non-hematologic** | Peripheral neuropathy | 9 (34.6%) | 1 (3.8%) | 7 (26.9%) | | 4 (15.4%) | |
| | Rash | 3 (11.5%) | | 3 (11.5%) | 1 (3.8%) | 1 (3.8%) | 1 (3.8%) |
| | Fatigue | 2 (7.7%) | 1 (3.8%) | | | | |
| | Constipation | 5 (19.2%) | | 4 (15.4%) | | 3 (11.5%) | |
| | Nausea | 3 (11.5%) | | | | | |
| | Anorexia | 5 (19.2%) | | 1 (3.8%) | | | |
| | Diarrhea | 2 (7.7%) | | 4 (15.4%) | | | |
| | Liver enzyme elevation | 3 (11.5%) | | 2 (7.7%) | 1 (3.8%) | 1 (3.8%) | |
| | Tumor lysis syndrome | | 1 (3.8%) | | | | |

Treatment delays occurred in 13 patients during induction therapy, most commonly due to neutropenia (n = 9), followed by thrombocytopenia (n = 3) and peripheral neuropathy (n = 1). During maintenance I,

treatment was delayed in 7 patients, with neutropenia being the predominant cause (n = 5), while rash and upper respiratory tract infection accounted for one case each. During maintenance II, treatment delays occurred in 2 patients, due to rash and pneumonia, respectively. The relative dose intensities (RDIs) of bortezomib and lenalidomide during induction were 88.0% and 88.7%, respectively. The RDI of daratumumab was 93.7% during maintenance I and 99.3% during maintenance II.

# DISCUSSION

In this multicenter phase II study, we evaluated six cycles of D-VRd induction followed by ASCT with two-year daratumumab and one-year lenalidomide maintenance in transplant-eligible patients aged 65–69 years with NDMM. All enrolled patients completed 6 cycles of induction, of whom 25 patients (96.2%) underwent ASCT. All patients who underwent ASCT achieved VGPR or better, and responses continued to deepen during maintenance. The overall MRD-negativity rate was 92.3%, and the 3-year PFS rate was 76.9%. The regimen was generally well tolerated, as no patient discontinued treatment due to AEs.

Evidence supporting D-VRd in elderly transplant-eligible patients has so far come mainly from subgroup analyses of randomized trials. In the GRIFFIN trial, 56 of 207 patients (27.1%) were aged ≥ 65 years, and the sCR rate was higher with D-VRd than with VRd regardless of age group (6). In the PERSEUS trial, the PFS benefit of D-VRd was less pronounced in patients aged ≥ 65 years (181/709, 25.5%) than in the overall population (HR, 0.97, 95% CI, 0.52–1.81)(7). A subsequent post hoc pooled analysis of patients aged ≥ 65 years in GRIFFIN and PERSEUS showed that D-VRd followed by D-R maintenance produced a ≥ CR rate of 82.8%, an MRD-negativity rate ($10^{-5}$) of 66.4%, a 12-month sustained MRD-negativity rate of 52.5%, and a 48-month PFS rate of 79.1% (9). However, patients aged ≥ 65 years treated with D-VRd had higher rates of grade ≥ 3 AEs (94.2% vs. 86.8%), and grade ≥ 3 infections (36.3% vs. 24.8%) than those treated with VRd, which were more pronounced than in the overall population. Nevertheless, rates of AEs leading to treatment discontinuation (40.8% vs. 45.6%) and fatal AEs (5.0% vs. 3.5%) were comparable between the two groups in elderly patients. In a real-world analysis by Joseph et al., 106 patients aged ≥ 65 years received four to six cycles of D-VRd induction followed by ASCT, and the 4-year PFS rate was 95%; the corresponding rate in patients aged < 65 years treated with D-VRd was 82% (12). In our study, the best ≥ CR rate was 96.2%, the overall MRD-negativity rate was 92.3%, and the 12-month sustained MRD-negativity rate was 65.4%, which are comparable to these data. The 4-year PFS rate was 71.0% (95% CI, 47.8–85.3). The detailed comparisons are shown in Table 3. With respect to safety, grade ≥ 3 neutropenia was the most common adverse event, occurring in 38.5% of patients during both induction and maintenance I, whereas grade ≥ 3 non-hematologic events, including infections, were infrequent, with grade ≥ 3 pneumonia observed in only one patient (3.8%). Treatment delays were mostly attributable to neutropenia, and dose intensity was well maintained. No treatment-related deaths occurred. Collectively, these findings support D-VRd induction followed by ASCT as a preferred frontline option for fit transplant-eligible patients aged 65 years or older and suggest that chronological age alone should not preclude this approach. Moreover, because Asian patients accounted for only 2.1% of the pooled analysis, our study provides prospective data on this strategy in an Asian population that has been underrepresented in pivotal trials.

Table 3
Outcomes of D-VRd and ASCT in patients aged ≥ 65 years across trials

| **Pooled analysis of GRIFFIN and PERSEUS studies (N = 120)** | **ISS-3/HRCA** | **≥ VGPR rate** | **PFS** | **MRD negative rate** | **≥ 12 months sustained MRD negative rate** |
|---|---|---|---|---|---|
| | **9.0%/22.7%)** | **93.5%** | **4-year 79.1%** | **66.4%** | **52.5%** |
| US real-world study (N = 106) | 21.0%/13.7% | 88.7% | 4-year 95% | NR | NR |
| The current study (N = 26) | 19.9%/34.6% | 100.0% | 4-year 71.0% | 92.3% | 65.4% |

ISS, international staging system; HRCA, high-risk cytogenetics; VGPR, very good partial response rate; PFS, progression free survival; MRD, minimal residual disease; NR, not reported

A distinctive feature of our study is that patients received six cycles of D-VRd induction before ASCT without post-transplant consolidation, because consolidation therapy is not reimbursed under the Korean health insurance system. Because the dosing schedule of D-VRd in our study was virtually identical to that in GRIFFIN, response rates at corresponding time points can be compared more directly. The ≥VGPR rate after four cycles of induction in our study (73.1%) was nearly identical to that at the end of induction in the D-VRd arm of GRIFFIN (71.7%). Likewise, after completion of six cycles of D-VRd, administered as six cycles of induction followed by ASCT in our study and as four cycles of induction followed by ASCT and two cycles of consolidation in GRIFFIN, the ≥VGPR rates were similar (96.2% vs. 90.9%). Taken together, these findings suggest that administering all D-VRd cycles before ASCT, rather than splitting them into pre-transplant induction and post-transplant consolidation, does not meaningfully compromise response, and that either sequence may be chosen according to patient and institutional circumstances.

In our study, maintenance therapy was limited to 2 years, and lenalidomide was discontinued after the first 12 months. This approach differs from the maintenance strategies used with daratumumab-based quadruplets in CASSIOPEIA (daratumumab every 8 weeks for up to 2 years), GRIFFIN (lenalidomide plus daratumumab every 4 weeks for up to 2 years), and PERSEUS (lenalidomide plus daratumumab every 4 weeks for at least 2 years, followed by response-adapted discontinuation of daratumumab). Although the optimal duration and composition of maintenance therapy have not yet been established, a recent report from PERSEUS showed that 73.3% of patients receiving daratumumab plus lenalidomide maintenance met the prespecified criteria for daratumumab discontinuation and remained off daratumumab for a median of 44 months (13). These observations suggest that a fixed-duration maintenance strategy, such as that used in our study, may be feasible following quadruplet induction although longer follow-up is needed.

The safety profile was consistent with the known profiles of the individual agents, and no new safety signals were identified. Grade ≥ 3 neutropenia occurred in 38.5% of patients during induction, compared

with 41.4% in the D-VRd arm of GRIFFIN and 62.1% in the D-VRd arm of PERSEUS (6, 7). Despite six cycles of twice-weekly subcutaneous bortezomib before ASCT, peripheral neuropathy of any grade occurred in 34.6% of patients during induction, and grade ≥ 3 neuropathy occurred in only one patient (3.8%). The corresponding rates were 59.6% and 7.1% in GRIFFIN and 53.6% and 4.3% in PERSEUS (6, 7). Nonetheless, one death of unknown cause occurred in a patient in CR, and one patient developed encephalopathy for which a daratumumab-related etiology was suspected. These events underscore the need for careful monitoring in elderly patients.

Our study has several limitations. First, the sample size was small and the study used a single-arm design without a control group. The comparisons with GRIFFIN and PERSEUS are therefore indirect cross-trial comparisons and should be interpreted with caution. Second, eligibility was restricted to patients aged 65–69 years who were deemed transplant-eligible by the investigators, and frailty was not formally assessed using a standardized geriatric assessment tool. Nevertheless, most patients completed all six cycles of induction and proceeded to ASCT with good treatment adherence, suggesting that investigators' judgment was adequate for identifying patients fit enough to tolerate this intensive approach. Finally, the MRD-negativity rates in our study should not be directly compared with those of GRIFFIN and PERSEUS, because MRD was assessed by next-generation flow cytometry rather than next-generation sequencing.

In conclusion, our findings suggest that six cycles of D-VRd induction followed by ASCT is a feasible and effective strategy for transplant-eligible patients aged 65–69 years with NDMM. This strategy achieved deep and sustained responses without compromising treatment adherence. Larger prospective studies with longer follow-up are warranted to validate these findings.

## Declarations

# Author contribution

All authors contributed to the study conception and design.

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# Data availability

Data used in the article is available from the corresponding author in case of reasonable request.

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# Figures

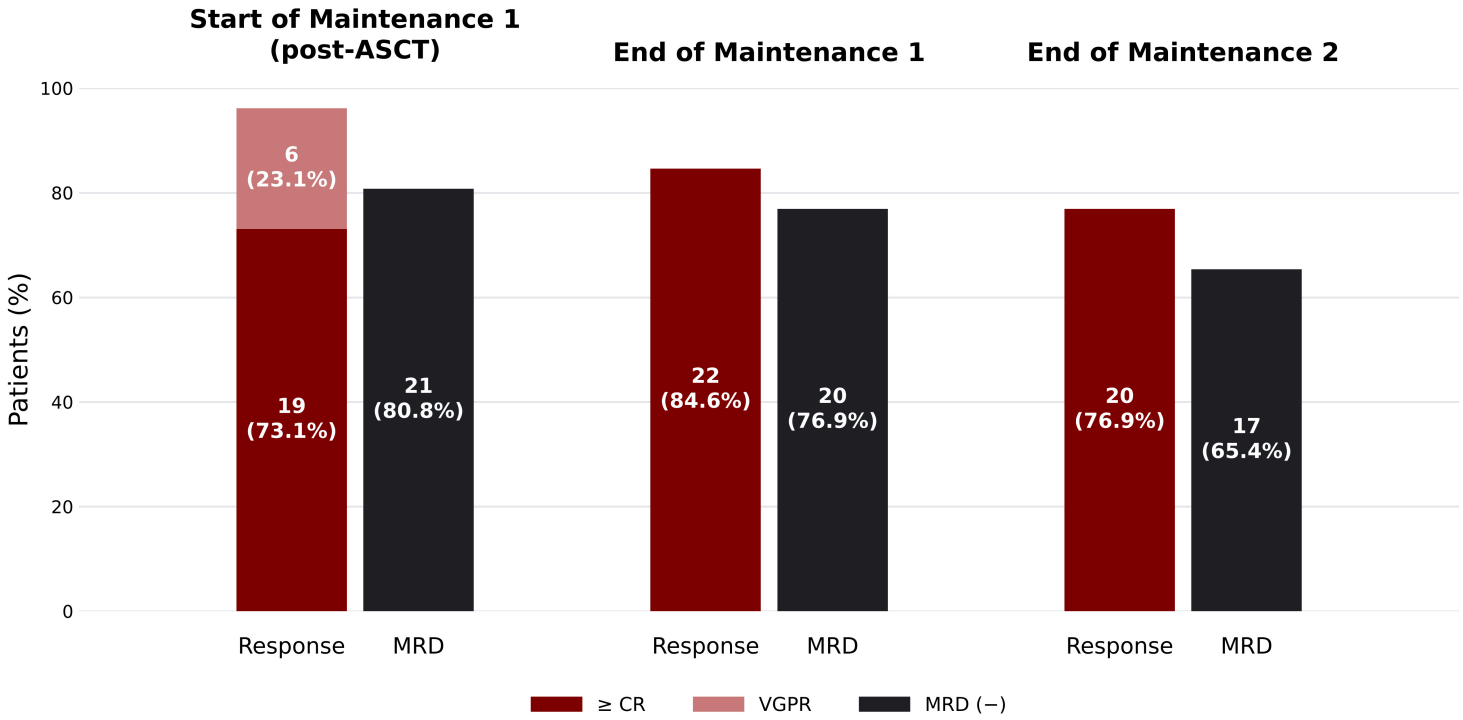



**Figure 2**

Conventional responses and minimal residual disease (MRD) negative rates at each assessment time point

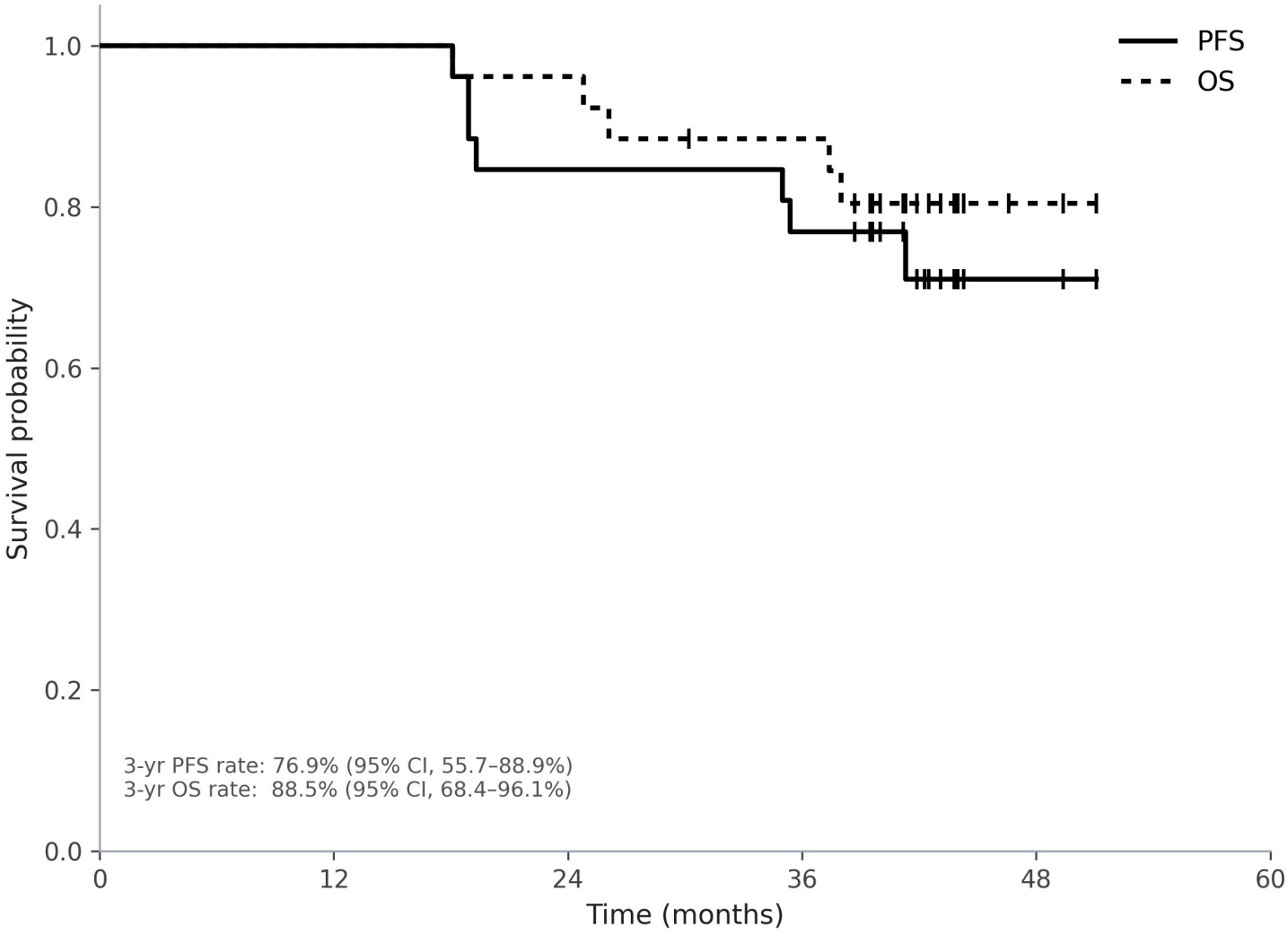



**Figure 3**

Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS)

## Supplementary Files

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- Supplementarymaterial.docx