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Abstract

Purpose: To evaluate clinical outcomes after maintenance therapy discontinuation in transplant-eligible multiple myeloma (MM) patients with measurable residual disease (MRD) negativity, identify predictors of post-discontinuation MRD resurgence, and assess salvage efficacy upon MRD recurrence.

Methods: This retrospective study enrolled 35 newly diagnosed MM patients treated at our center between January 2010 and January 2024. Patients received novel-agent induction, autologous stem cell transplantation, and maintenance therapy, which ceased after MRD negativity, were confirmed by multiparameter flow cytometry. The primary endpoint was MRD resurgence. Fine–Gray competing-risk regression was used to identify associated factors. Kaplan–Meier methods estimated treatment-free survival (TFS) and overall survival (OS).

Results: Median patient age was 53 years (range 35–67). Median duration from MRD negativity to maintenance cessation was 32.0 months; median post-discontinuation follow-up was 79.0 months. Fifteen patients (42.9%) developed MRD resurgence; 3- and 5-year cumulative incidence rates were 26.9% (95% CI 13.4–42.5%) and 37.4% (95% CI 21.1–53.8%), respectively. Using multivariable Fine-Grey analysis, high-risk cytogenetic abnormalities (HRCA)predicted higher MRD resurgence risk (HR 4.8, 95% CI 1.6–14.6, P=0.005), whereas sustained MRD negativity ≥2 years before discontinuation reduced risk (HR 0.2, 95% CI 0.1–0.7, P=0.012). Of 15 patients with MRD resurgence, 13 received salvage therapy and 10 (76.9%) regained MRD negativity. Median post-discontinuation TFS and OS were 67.3 and 80.0 months, respectively.

Conclusion: Maintenance discontinuation after MRD negativity is feasible in selected transplant-eligible MM patients. HRCA and sustained MRD negativity duration facilitate post-stop risk stratification. These exploratory findings require validation in larger multicenter cohorts.

Keywords: multiple myeloma; measurable residual disease; maintenance therapy; treatment discontinuation; autologous stem cell transplantation; competing-risk analysis

1 Introduction

Multiple myeloma (MM) is a malignant hematologic disorder characterized by the clonal proliferation of plasma cells within the bone marrow. Despite substantial advances in the development of therapeutic strategies, MM is still generally regarded as incurable (van de Donk et al. 2021). Over the past two decades, the development and introduction of novel agents has markedly improved the depth of response and long-term survival of patients with MM. Particularly, among transplant-eligible patients, quadruplet induction regimens that incorporate an anti-CD38 monoclonal antibody have further increased deep response rates, allowing an increasing proportion of patients to achieve a complete response (CR) and even measurable residual disease (MRD) negativity (Facon et al. 2024; Sonneveld et al. 2024). Moreover, the prolonged disease control achieved with modern therapy has prompted renewed consideration of the need for and optimal duration of long-term treatment.

Currently, maintenance therapy after autologous stem cell transplantation (ASCT) is the standard of care for patients with newly diagnosed MM (NDMM), particularly lenalidomide-based regimens, which are generally recommended until disease progression (Richardson et al. 2022). This strategy is supported primarily by the results of randomized controlled trials—including CALGB 100104 (Holstein et al. 2017), IFM 2005-02 (Attal et al. 2010), and Myeloma XI (Jackson et al. 2019)—which have demonstrated that lenalidomide-based maintenance significantly prolongs progression-free survival (PFS) over observation alone or placebo, even achieving an overall survival (OS) benefit in some studies (McCarthy et al. 2012). However, most of these trials were conducted before the widespread adoption of triplet/quadruplet induction regimens and before MRD assessment became an integral component in evaluating treatment responses. Therefore, in the current era of highly effective frontline therapy, the appropriateness of the traditional “maintenance until progression” approach for all patients who achieve deep responses warrants further investigation (Derman et al. 2024; Gan et al. 2026; Sato et al. 2025, 2026).

To this end, the potential benefits of prolonged maintenance therapy must be weighed against its cumulative treatment burden. Continuous exposure to immunomodulatory agents may increase the risks of cytopenias, infections, fatigue, thromboembolic events, and second primary malignancies (SPMs). In addition, maintenance of treatment over the long term may adversely affect the health-related quality of life of the patient and impose a substantial financial burden on the patients and on healthcare systems (Badros et al. 2025; Sneider and Derman 2025). Consequently, there is a pressing need to develop individualized maintenance strategies according to the specific disease biology and depth of response and to address critical clinical questions, including which patients may safely discontinue therapy and when discontinuation is appropriate.

The implementation of MRD assessment has provided new opportunities to address these questions. As one of the strongest prognostic biomarkers of MM, MRD status is closely associated with PFS and OS, and its predictive value has been validated across different treatment regimens and disease settings (Paiva et al. 2025). Importantly, compared with a single MRD-negative assessment, a sustained MRD-negative assessment appears to have greater prognostic value, suggesting that longitudinal MRD dynamics may serve as a useful tool to guide treatment escalation or de-escalation (Perrot et al. 2025; Sneider and Derman 2025). On this basis, several exploratory studies have investigated MRD-guided maintenance discontinuation (Goldschmidt et al. 2020). The results of studies, including MRD2STOP (Derman et al. 2024), MASTER and a Greek prospective cohort study (Terpos et al. 2025), have suggested that maintenance therapy discontinuation may be feasible in select patients who achieve deep and sustained MRD negativity, with some even maintaining prolonged treatment-free survival

(TFS). These findings provide preliminary support for shifting from the traditional "continuous treatment" paradigm toward an MRD-driven, response-adapted approach (Giri et al. 2025).

Nevertheless, the evidence supporting MRD-guided maintenance discontinuation remains limited. Most available studies are single-center, prospective cohorts with small sample sizes, and substantial heterogeneity exists in terms of discontinuation criteria, MRD assessment method, and follow-up strategy (Meseha et al. 2024; Paiva et al. 2025). Therefore, we conducted a retrospective, real-world study drawing on 16 years of clinical experience at our institution to evaluate transplant-eligible patients with MM who underwent ASCT and discontinued maintenance therapy after achieving MRD negativity. The primary objectives were to determine the incidence of MRD resurgence after discontinuation and to identify the associated risk factors. We further examined the patterns of disease progression after MRD resurgence and the outcomes of subsequent salvage therapy. This study aims to provide real-world evidence to inform patient selection, risk stratification, and clinical decision-making for MRD-guided maintenance discontinuation and thereby contribute to the development of more precise and individualized treatment strategies for MM.

2 Materials and Methods

2.1 Study Design and Patients

This was a single-center, retrospective, observational study. Clinical data were collected from 35 patients with NDMM treated at our institution between January 2010 and January 2024. The patients were followed until January 1, 2026.

The eligibility criteria were as follows: (1) a diagnosis of NDMM according to the International Myeloma Working Group (IMWG) criteria (Rajkumar et al. 2014), which are based on clinical manifestations, laboratory findings, and the results of bone marrow pathologic evaluation; (2) treatment with novel agent–based induction therapy; (3) subsequent treatment with ASCT; (4) treatment with maintenance therapy after ASCT; (5) achievement of MRD negativity, confirmed by at least two consecutive bone marrow MRD assessments via multiparameter flow cytometry (MFC); (6) discontinuation of maintenance therapy after the achievement of MRD negativity according to patient preference or physician judgement coupled with regular monitoring of disease status and MRD dynamics during the treatment-free period; and (7) available complete clinical and follow-up data. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee.

2.2 MRD Assessment

All patients underwent serial bone marrow MRD monitoring according to a standardized institutional protocol. Assessments were performed 3, 6, 9, 12, 18, and 24 months after ASCT and every 6–12 months thereafter, depending on disease status. After maintenance was discontinued, the frequency of MRD monitoring was adjusted on the basis of clinical circumstances, with intervals ranging from 1 to 24 months.

Bone marrow MRD was evaluated via MFC. Bone marrow aspirates (3–5 mL) were collected into EDTA-anticoagulated tubes; the first-pull aspirate was preferentially used to minimize hemodilution. The samples were subject to red-cell lysis with ammonium chloride, washing in phosphate-buffered saline (PBS), and antibody staining.

A standardized eight-color, two-tube panel was used to evaluate the bone marrow MRD. Tube 1 contained cKappa, cLambda, CD19, CD20, CD138, CD45, CD38, and CD56; Tube 2 contained CD19, CD20, CD138, CD45, CD56, CD38, CD117, and CD81. MRD analysis was performed according to a sequential gating

strategy: (1) identification of valid events on the basis of CD45 expression and time parameters; (2) exclusion of doublets using FSC-H/FSC-A and SSC-H/SSC-A; (3) removal of debris on the basis of FSC/SSC characteristics; (4) identification of plasma-cell populations according to the expression of CD38 and CD138; and (5) detection of aberrant clonal plasma cells on the basis of abnormal immunophenotypic patterns and immunoglobulin light-chain restriction. MRD levels were expressed as the proportion of aberrant clonal plasma cells among total nucleated cells. At least 2×10^6 events were acquired and analyzed per sample. MRD positivity was defined as the detection of ≥20 aberrant clonal plasma cells, corresponding to a sensitivity of 1×10^{-5}. All assessments were performed under standardized laboratory conditions, including regular instrument calibration, antibody validation, and internal quality control.

2.3 Definitions, Follow-Up, and Study Endpoints

High-risk cytogenetic abnormalities (HRCAs) were defined as the presence of any of the following: del(17p), 1q amplification, t(4;14), or t(14;16). Patients with ≥2 HRCAs were classified as having ultrahigh-risk cytogenetic abnormalities (UHRCAs).

MRD resurgence was defined as the reappearance of detectable residual disease after maintenance discontinuation in patients with previously confirmed MRD negativity—specifically, the detection of ≥20 aberrant plasma cells per 2×10^6 analyzed events, confirmed with repeat testing. The primary endpoints were (1) the incidence of MRD resurgence after maintenance discontinuation and (2) the identification of risk factors associated with MRD resurgence. Secondary endpoints included (1) treatment-free survival (TFS) after discontinuation, (2) overall survival (OS), and (3) salvage therapy efficacy after MRD resurgence. TFS was defined as the interval from maintenance discontinuation to the initiation of subsequent antimyeloma therapy and was censored at death or the time of the last follow-up. OS was defined as the interval from maintenance discontinuation to death from any cause or the time of the last follow-up.

2.4 Statistical Analysis

Continuous variables are summarized as medians with ranges or interquartile ranges (IQRs), and categorical variables are summarized as frequencies and percentages. For between-group comparisons, the Mann–Whitney U test was used for continuous variables, and the chi-square test or Fisher's exact test, as appropriate. was used for categorical variables. TFS and OS were estimated via the Kaplan–Meier method, including the estimation of median survival times and calculation of survival rates at predefined time points. Because nonprogression death could preclude the occurrence of MRD resurgence, Fine–Grey competing-risk regression models were constructed to evaluate factors associated with MRD resurgence, with nonprogression death treated as a competing event. Variables that were statistically significant or clinically relevant were entered into multivariable models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were subsequently calculated, and cumulative incidence function (CIF) curves were generated to illustrate the probability of MRD resurgence over time. All analyses were performed with R version 4.3.0, and a two-sided P value <0.05 was considered to indicate statistical significance.

3 Results

3.1 Baseline Characteristics

The baseline clinical characteristics of the 35 patients included in this study are summarized in Table 1. The median age at diagnosis was 53 years (range, 35–67); 25 patients (71.4%) were male, and 10 (28.6%) were female. Four patients (11.4%) were aged ≥65 years at diagnosis.

Table 1 Baseline clinical characteristics of the 35 patients with TE-NDMM who discontinued maintenance therapy after achieving MRD negativity

Characteristic	***n***	**%**
Sex		
Male	25	71.4
Female	10	28.6
Median age at diagnosis (range), years	53	35–67
Age ≥65 years	4	11.4
M-protein type		
IgG	12	34.3
IgA	4	11.4
IgD	1	2.9
Light chain	18	51.4
Hemoglobin ≤100 g/L	16	45.7
Platelets ≤100 × 10^9/L	1	2.9
Renal impairment	14	40.0
LDH level ≥240 U/L	8	22.9
Serum calcium level ≥2.8 mmol/L	2	5.7
Extramedullary disease, positive	9	25.7
HBsAg, positive	5	14.3
Median bone marrow plasma cells (range), %	20.0	1.0–70.0
R-ISS stage		
I	12	34.3
II	18	51.4
III	5	14.3
Cytogenetic abnormalities		
del(13q)	10	28.6
1q21 gain/amplification	9	25.7
t(11;14)	2	5.7
t(4;14)	2	5.7
t(14;16)	2	5.7
del(17p)	1	2.9
High-risk (HRCA)	8	22.9
Ultrahigh-risk (UHRCA)	0	0

Abbreviations: TE-NDMM, transplant-eligible newly diagnosed multiple myeloma; MRD, measurable residual

disease; LDH, lactate dehydrogenase; HBsAg, hepatitis B surface antigen; R-ISS, Revised International Staging System; HRCAs, high-risk cytogenetic abnormalities; UHRCAs, ultrahigh-risk cytogenetic abnormalities. HRCAs were defined as del(17p), 1q amplification, t(4;14), and t(14;16).

With respect to the immunoglobulin subtypes, light-chain MM was the most common (18 patients, 51.4%), followed by IgG MM (12 patients, 34.3%), IgA MM (4 patients, 11.4%), and IgD MM (1 patient, 2.9%). According to the Revised International Staging System (R-ISS), 12 patients (34.3%) had stage I disease, 18 (51.4%) had stage II disease, and 5 (14.3%) had stage III disease.

At the time of diagnosis, 14 (40.0%) had renal impairment, and 8 (22.9%) had elevated levels of lactate dehydrogenase (LDH; ≥240 U/L). Extramedullary disease (EMD) was present in 9 patients (25.7%). The median bone marrow plasma-cell proportion at diagnosis was 20.0% (range, 1.0–70.0%). Cytogenetic abnormalities included del(13q) in 10 patients (28.6%); 1q21 gain/amplification in 9 patients (25.7%), including 3 with amplification., t(11;14), t(4;14), and t(14;16) in 2 patients each (5.7%), and del(17p) in 1 patient (2.9%). Overall, 8 patients (22.9%) were classified as having HRCAs. No patients with double- or triple-hit myeloma were identified in this cohort.

3.2 Treatment Characteristics and Maintenance Discontinuation

The characteristics of the treatment regimens and maintenance discontinuation are summarized in Table 2. All patients received bortezomib-based induction therapy, and none of the patients received quadruplet induction therapy involving an anti-CD38 monoclonal antibody. Thirty-two patients (91.4%) received triplet-based induction therapy, and 3 (8.6%) received doublet regimens. No patients underwent tandem ASCT. The maintenance strategies were heterogeneous; the most common regimens were interferon-based therapy (12 patients, 34.3%), thalidomide-based therapy (12 patients, 34.3%), thalidomide combined with interferon (5 patients, 14.3%), lenalidomide-based therapy (2 patients, 5.7%), proteasome inhibitor (PI)–containing regimens (3 patients, 8.6%), and daratumumab-containing therapy (1 patient, 2.8%).

Table 2 Treatment regimens and maintenance discontinuation characteristics of the 35 patients

Variable	***n***	**%**
Induction therapy (all bortezomib-based)		
Doublet regimen	3	8.6
Triplet regimen	32	91.4
Tandem transplantation	0	0
Maintenance regimen		
Interferon	12	34.3
Thalidomide	12	34.3
Thalidomide + interferon	5	14.3
Lenalidomide	2	5.7
PI-containing	3	8.6
Daratumumab-containing	1	2.8
Timing of bone marrow MRD negativity		

Variable	*n*	%
During induction	17	48.6
During maintenance	18	51.4
Discontinuation within 2 years of MRD negativity	8	22.9
Reason for discontinuation		
Patient preference	25	71.4
Second primary malignancy	10	28.6

Abbreviations: MRD, measurable residual disease; PI, proteasome inhibitor. All induction regimens were bortezomib-based.

With respect to the timing of MRD negativity, 17 patients (48.6%) achieved MRD negativity during induction therapy, and 18 (51.4%) achieved MRD negativity during maintenance therapy. Eight patients (22.9%) discontinued maintenance therapy within 2 years of achieving MRD negativity. Regarding the reasons for discontinuation, 25 patients (71.4%) discontinued treatment on their own, whereas 10 (28.6%) discontinued treatment because of a second primary malignancy, including acute leukemia, myelodysplastic syndrome, or a solid tumor.

3.3 Risk Factors Associated with MRD Resurgence After Maintenance Discontinuation

The median interval from the achievement of MRD negativity to maintenance discontinuation was 32.0 months (range, 0.3–143.2), and the median follow-up after discontinuation was 79.0 months (range, 3.8–113.0). During follow-up, 15 patients (42.9%) developed MRD resurgence, and 9 (25.7%) died without disease progression. Among the 15 patients with MRD resurgence, the median time to resurgence was 22.4 months (IQR, 12.1–44.3; range, 3.4–98.0).

In the Fine–Grey competing-risk model that treated nonprogression death as a competing event, the cumulative incidence of MRD resurgence 3 and 5 years after discontinuation was 26.9% (95% CI, 13.4%–42.5%) and 37.4% (95% CI, 21.1%–53.8%), respectively (Fig. 1a).

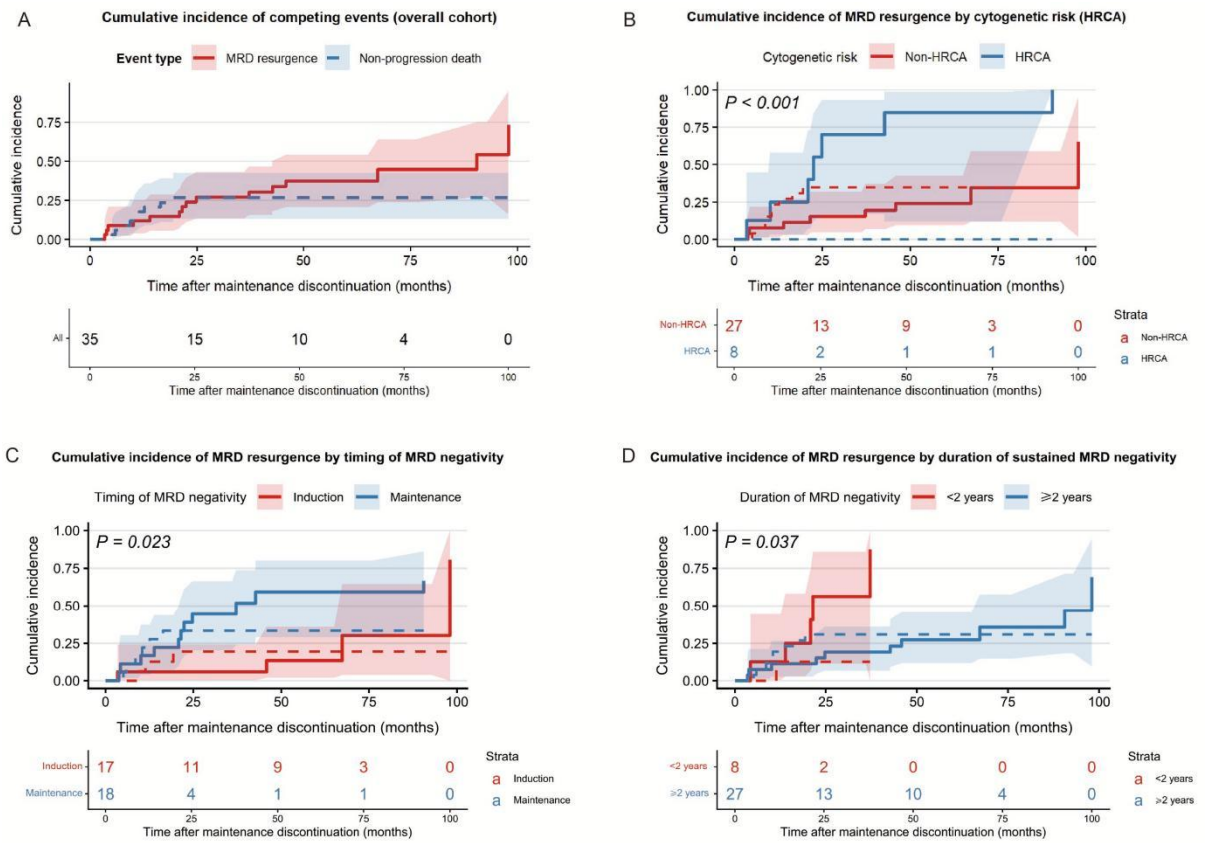


Fig. 1 Cumulative incidence of measurable residual disease (MRD) resurgence after maintenance discontinuation, estimated using Fine–Grey competing-risk models with nonprogression death (death without disease progression) as the competing event. (**a**) Cumulative incidence of the two competing events in the overall cohort (n = 35). (**b–d**) Cumulative incidence of MRD resurgence stratified by (**b**) cytogenetic risk (non-HRCAs vs. HRCAs), (**c**) timing of MRD negativity (during induction vs. during maintenance), and (**d**) duration of sustained MRD negativity before discontinuation (<2 vs. ≥2 years). *Abbreviations:* MRD, measurable residual disease; HRCAs, high-risk cytogenetic abnormalities

Univariable and multivariable Fine-Grey analyses were performed to identify factors associated with MRD resurgence (Table 3). The results of univariable analysis revealed that HRCAs and the achievement of MRD negativity during maintenance were associated with a higher risk of MRD resurgence. Specifically, patients with HRCAs had a significantly greater risk of resurgence (HR, 5.6; 95% CI, 2.1–14.9; P<0.001), as did patients who achieved MRD negativity during maintenance (HR, 3.4; 95% CI, 1.2–9.8; P=0.023). Among the 15 patients with MRD resurgence, 7 (46.7%) had at least one HRCA at diagnosis. The 36-month cumulative incidence of MRD resurgence was 70.0% (95% CI, 29.6%–100.0%) in patients with HRCAs *versus* 15.3% (95% CI, 1.1%–29.4%) in those without. Patients who achieved MRD negativity during maintenance had a higher 36-month cumulative incidence of resurgence than did those who achieved it during induction therapy (44.4% vs. 5.9%; 95% CI, 20.0%–68.9% vs. 0%–17.4%). In contrast, maintenance discontinuation after sustained MRD negativity for ≥2 years was associated with a lower risk of MRD resurgence (HR, 0.3; 95% CI, 0.1–0.9; P=0.037). Similarly, patients who had been MRD negative for <2 years before maintenance discontinuation had a greater cumulative incidence of resurgence than those who had been MRD negative for ≥2 years (56.2% vs. 19.0%) (Fig. 1b–d). In the

multivariable Fine–Grey model, HRCAs remained independently associated with a higher risk of MRD resurgence after maintenance discontinuation (HR, 4.8; 95% CI, 1.6–14.6; P=0.005), whereas sustained MRD negativity for ≥2 years before discontinuation remained independently associated with a lower risk of resurgence (HR, 0.2; 95% CI, 0.1–0.7; P=0.012).

Table 3 Fine–Gray competing-risk regression analysis of factors associated with MRD resurgence after maintenance discontinuation

Variable	Category	Univariable HR	95% CI	*P*	Multivariable HR	95% CI	*P*
Age	≥65 years	2.1	0.4–10.3	0.350	—	—	—
Sex	Male	1.5	0.4–5.5	0.510	—	—	—
Amyloidosis	Present	2.5	0.4–10.0	0.290	—	—	—
R-ISS	Stage II/III	1.0	0.4–2.7	0.950	—	—	—
Light-chain type	Yes	0.9	0.3–2.3	0.770	—	—	—
EMD	Positive	1.1	0.3–3.3	0.900	—	—	—
HRCAs	**Positive**	**5.6**	**2.1–14.9**	**<0.001**	**4.8**	**1.6–14.6**	**0.005**
Timing of MRD negativity	During maintenance	**3.4**	**1.2–9.8**	**0.023**	2.0	0.5–7.1	0.300
Maintenance regimen	Thalidomide/interferon	1.6	0.4–6.2	0.520	—	—	—
Duration of MRD negativity	**≥2 years**	**0.3**	**0.1–0.9**	**0.037**	**0.2**	**0.1–0.7**	**0.012**

Estimates were derived from Fine–Gray competing-risk regression analysis, with nonprogressive death treated as a competing event. *Abbreviations:* HR, hazard ratio; CI, confidence interval; R-ISS, Revised International Staging System; EMD, extramedullary disease; HRCAs, high-risk cytogenetic abnormalities; MRD, measurable residual disease. Dashes indicate variables that were not entered into the multivariable model.

3.4 MRD Resurgence, Clinical Progression, and Salvage Treatment Outcomes

At the last follow-up (January 1, 2026), 15 of the 35 patients (42.9%) who discontinued maintenance had experienced MRD resurgence. Among these patients, 2 (13.3%) had experienced MRD resurgence without evidence of progressive disease (PD), whereas the remaining 13 (86.7%) had experienced MRD resurgence alongside obvious clinical or biochemical progression. The median TFS was 67.3 months (95% CI, 26.9–98.0), and the estimated TFS rates at 1, 3, and 5 years after discontinuation were 89.9%, 71.0%, and 54.9%, respectively (Fig. 2a).

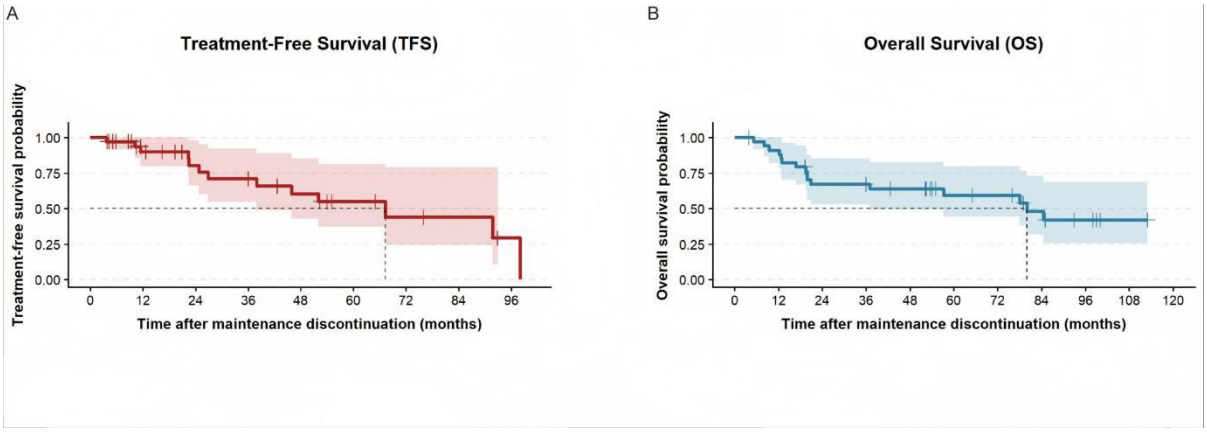


Fig. 2 Kaplan–Meier estimates of treatment-free (TFS) and overall survival (OS) after maintenance discontinuation in the overall cohort (n = 35). (**a**) Treatment-free survival and (**b**) overall survival, both of which were calculated from the date of maintenance discontinuation. The median TFS was 67.3 months (95% CI, 26.9–98.0), and the median OS was 80.0 months (95% CI, 20.9–not reached). *Abbreviations:* TFS, treatment-free survival; OS, overall survival; CI, confidence interval

Among the 15 patients who experienced MRD resurgence, 2 (13.3%) did not undergo subsequent antimyeloma therapy because of personal preference, whereas 13 (86.7%) received salvage treatment after disease progression. The salvage regimens and outcomes are summarized in Table 4. The most common regimen used was PAD (bortezomib, liposomal doxorubicin, and dexamethasone), which was administered to 8 patients (61.5%). Other regimens used included KAPD (carfilzomib, liposomal doxorubicin, pomalidomide, and dexamethasone) in 2 patients (15.4%), VRCD (bortezomib, lenalidomide, cyclophosphamide, and dexamethasone) in 1 patient (7.7%), daratumumab-containing Dara-KPD in 1 patient (7.7%), and B-cell maturation antigen (BCMA)–targeted CAR T-cell therapy in 1 patient (7.7%). In addition, 5 patients (38.5%) underwent a salvage second ASCT after the initial salvage therapy. Among the 13 patients who received salvage treatment, 10 (76.9%) subsequently achieved MRD negativity again.

Table 4 Salvage regimens and outcomes in 13 patients with MRD resurgence after maintenance discontinuation

Salvage regimen	***n***	**%**
Salvage regimen distribution (n = 13)		
PAD	8	61.5
KAPD	2	15.4
VRCD	1	7.7
Dara-KPD	1	7.7
BCMA-targeted CAR T-cell therapy	1	7.7
Salvage second autologous stem cell transplantation	5	38.5
Salvage outcome		
Reachievement of MRD negativity	10	76.9

Percentages are calculated for the 13 patients who received salvage therapy. *Abbreviations:* PAD, bortezomib/liposomal doxorubicin/dexamethasone; KAPD, carfilzomib/liposomal

doxorubicin/pomalidomide/dexamethasone; VRCD, bortezomib/lenalidomide/cyclophosphamide/dexamethasone; Dara-KPD, daratumumab/carfilzomib/pomalidomide/dexamethasone; BCMA, B-cell maturation antigen; MRD, measurable residual disease.

Survival outcomes were analyzed from the date of maintenance discontinuation. The median OS for the entire cohort was 80.0 months (95% CI, 20.9–not reached), and the estimated OS rates at 1, 3, and 5 years after discontinuation were 91.2%, 67.2%, and 59.4%, respectively (Fig. 2b). Among the patients who received salvage therapy after MRD resurgence, the median follow-up after retreatment was 43.3 months (95% CI, 15.0–not reached). The median OS from the initiation of salvage therapy was 74.5 months (95% CI, 23.1–80.8), and the 1-, 3-, and 5-year OS rates after retreatment were 86.2%, 67.0%, and 53.6%, respectively.

4 Discussion

The continuation of maintenance therapy until disease progression after ASCT has long been regarded as the standard treatment strategy for transplant-eligible MM patients. However, previous studies have shown that a subset of patients can achieve prolonged disease control even without such maintenance therapy. A retrospective study from the Mayo Clinic (Derman 2023; Sneider and Derman 2025) revealed that approximately 9% of patients achieved disease control for more than 8 years after ASCT without continuation of maintenance therapy, with a median PFS of 13.8 years and a median OS of 19.9 years—indicative of considerable biological heterogeneity among patients with MM and that some individuals may maintain long-term remission without continuous treatment. Nonetheless, in the absence of reliable risk stratification tools, discontinuation according to disease status was uncommon before the widespread adoption of MRD assessment.

In recent years, advances in quadruplet induction regimens and MRD detection have led to a reappraisal of the optimal duration of maintenance therapy. The results of the CASSIOPEIA study revealed that daratumumab maintenance improved PFS, although the additional benefit appeared limited among patients who had already received daratumumab during induction therapy; moreover, some patients who achieved MRD negativity in the observation arm maintained prolonged disease control (Paiva and San-Miguel 2025). The results of the PERSEUS study (Rodríguez-Otero et al. 2024) further demonstrated that MRD negativity rates after treatment with Dara-VRd improved mainly during the early phase of maintenance and plateaued after approximately 2 years, suggesting that the incremental benefit of prolonged maintenance may diminish as deeper responses are achieved. Accordingly, in the era of modern MM therapy, maintenance strategies are gradually shifting from a conventional "treat until progression" approach towards individualized strategies guided by disease risk and MRD dynamics. Identifying patients who may safely discontinue therapy and determining an appropriate time to do so have become important questions in the precision management of MM.

In this study, we retrospectively analyzed the long-term outcomes of 35 patients with NDMM who achieved bone marrow MRD negativity after ASCT and subsequently discontinued maintenance therapy; the data were drawn from 16 years of single-center, real-world data. Fine–Grey competing-risk models were used to examine factors associated with MRD resurgence after discontinuation, and clinical outcomes and salvage-treatment responses after resurgence were evaluated. We found that HRCAs were associated with a higher risk of MRD resurgence after discontinuation, whereas discontinuation after sustained MRD negativity for ≥2 years was associated with a lower risk. In addition, among patients who experienced MRD resurgence and received salvage

therapy, a substantial proportion subsequently achieved MRD negativity again. Given the limited sample size, these findings should be regarded as exploratory and therefore require validation in larger, multicenter studies; nonetheless, our study provides clinically relevant real-world evidence for risk assessment and patient selection in MRD-guided maintenance discontinuation.

One notable observation in our study was the potential influence of HRCAs on outcomes after maintenance discontinuation. This finding is consistent with those of previous reports suggesting that adverse cytogenetic features may constitute a risk factor beyond MRD status itself. The results of a pooled analysis of the GRIFFIN and MASTER studies (Costa et al. 2023; Voorhees et al. 2020) revealed that patients with ≥2 HRCAs had a relatively unfavorable 3-year PFS despite the use of intensive treatment and MRD-guided strategies (52.4% and 53.5%, respectively), suggesting that high-risk genetic abnormalities may reflect an adverse disease biology that is not fully captured by MRD negativity alone. Similarly, the results of the IFM-2009 study (Perrot et al. 2020) indicated inferior disease control among high-risk patients after limited-duration maintenance than among standard-risk patients. Given these observations, the discontinuation of maintenance therapy solely on the basis of a negative MRD result on conventional flow cytometry may warrant additional caution in patients with HRCAs.

For patients with HRCAs, future decisions regarding discontinuation may require the integration of multiple risk indicators, including a longer duration of sustained MRD negativity, and the use of more sensitive MRD assessment methods (such as next-generation sequencing or highly sensitive next-generation flow cytometry) and complementary imaging, such as PET-CT, to exclude residual extramedullary disease. For ultrahigh-risk patients, the evidence supporting routine discontinuation remains insufficient, given their substantial risk of relapse. In our cohort, no patients had double- or triple-hit MM, and only 8 patients (22.9%) had a single HRCA. As no ultrahigh-risk patients were included in our cohort, the safety of maintenance discontinuation in this population could not be addressed and thus warrants dedicated investigations. The results of studies evaluating intensified approaches for ultrahigh-risk populations—including GMMG-CONCEPT (Leypoldt et al. 2025), OPTIMUM (Kaiser et al. 2024), and IFM 2018-04 (Touzeau et al. 2022)—have suggested that prolonged treatment intensification may improve disease control; nevertheless, this population should continue to be studied in prospective clinical trials.

Another important observation from our cohort was that discontinuation after sustained MRD negativity for ≥2 years was associated with a lower risk of MRD resurgence. This factor remained independently protective in the multivariable analysis, suggesting that prolonged, deep remission may be associated with more durable disease control after maintenance discontinuation. These observations are consistent with those of previous studies. In the GEM2014MAIN study (Guerrero et al. 2024), patients who maintained MRD negativity at a sensitivity of 10^{-6} after 24 cycles of maintenance treatment and subsequently discontinued treatment achieved a 4-year PFS rate of 82.8% after discontinuation, which was significantly greater than that of patients with persistent MRD positivity (50.4%; HR, 0.25; P<0.0001). In the MRD2STOP study (Derman et al. 2024), patients who discontinued maintenance after a median of 36 months of treatment and had achieved deep MRD negativity maintained favorable outcomes, with a 3-year PFS rate of 85–92%. Furthermore, in the Greek cohort study reported by Terpos et al., in which patients received triplet induction, ASCT, and lenalidomide maintenance, followed by discontinuation after 3 years of maintenance when both bone marrow and imaging-based MRD assessments remained negative, the 3-year treatment-free survival rate after discontinuation was 75.8%, and the 7-year PFS rate (from diagnosis) reached 90.2% (Terpos et al. 2025). Collectively, these findings suggest that

sustained, stable, deep MRD negativity may be an important factor for identifying patients suitable for discontinuation. However, the optimal duration of MRD negativity required before discontinuation remains undefined; in our study, a threshold of ≥2 years appeared to have desirable predictive value but requires further validation in larger cohorts.

In the present study, patients who achieved MRD negativity only during maintenance had a higher risk of MRD resurgence according to univariable analysis; however, this association was attenuated and no longer statistically significant after multivariable adjustment. These findings suggest that the timing of MRD conversion may reflect differences in treatment sensitivity, baseline disease burden, or underlying disease biology among patients. The results of previous studies, including PETHEMA/GEM2012MENOS65 and FORTE (D'Agostino et al. 2024; Guerrero et al. 2024), suggest that patients who achieve early MRD negativity tend to have more favorable long-term disease control. However, given the limited sample size of our cohort, potential interactions between the timing of MRD conversion and other prognostic factors—such as HRCA status and duration of MRD negativity—cannot be excluded. The independent prognostic value of the timing of MRD conversion therefore requires further investigation.

A major clinical concern regarding MRD-guided maintenance discontinuation is whether disease recurrence after therapy cessation compromises the efficacy of subsequent treatments. Our study provides real-world evidence on this issue: among the 15 patients with MRD resurgence, 13 (86.7%) had concomitant clinical or biochemical progression, suggesting that, at the 10^{-5} sensitivity threshold used in our study, MRD resurgence more often represented a marker of disease reactivation than a prolonged early warning signal. These observations underscore the potential value of more sensitive MRD detection for identifying earlier biological relapse. Notably, among patients who received salvage therapy, 10 (76.9%) subsequently achieved MRD negativity again, indicating that recurrence after discontinuation does not necessarily imply a lost therapeutic opportunity. Several patients achieved deep responses through combination regimens containing novel agents, salvage ASCT, or emerging immunotherapies. Under close monitoring, therefore, discontinuation should not be equated with treatment abandonment but rather viewed as a dynamic management strategy in which treatment intensity is adapted to disease evolution (Costa et al. 2023). These findings offer additional insights into how the potential risks and benefits of MRD-guided discontinuation can be balanced.

The maintenance regimens used in our cohort reflect real-world practice and differed among the patients; they included interferon-, thalidomide-, lenalidomide-, and PI-based regimens as well as daratumumab-containing strategies. No significant association was observed between the type of maintenance regimen and the risk of MRD resurgence, suggesting that, among patients who have already achieved MRD negativity, subsequent disease control after discontinuation may be influenced more by the underlying disease biology and depth of response than by the specific maintenance regimen administered. However, the impact of different maintenance approaches requires further investigation in larger cohorts. In addition, 28.6% of the patients discontinued maintenance treatment because of secondary malignancies or other long-term treatment-related concerns, highlighting the clinical relevance of cumulative toxicity during long-term therapy. The incidence of second primary malignancies in our cohort was higher than that reported in previous studies, such as the Myeloma XI trial, which reported an incidence of 7.7% in the posttransplant lenalidomide maintenance group (Jackson et al. 2019). However, because of the retrospective design, a causal relationship between maintenance therapy and secondary malignancies cannot be established. These findings emphasize the importance of balancing the potential benefits of prolonged disease

control against the long-term treatment burden in patients with extended survival.

Several limitations of this study should be acknowledged. First, this was a single-center, retrospective study with a relatively small sample size (n=35), and the limited number of MRD-resurgence events may have reduced the statistical power of the risk factor analyses. Although the size of the cohort was comparable to that of previously published studies in this field (e.g., MRD2STOP [n=47] and selected MASTER cohorts (Costa et al. 2023; Derman et al. 2024)), our findings should be considered exploratory and hypothesis-generating rather than definitive. Second, discontinuation was not determined according to a uniform prospective protocol but was influenced by patient preference, treatment-related adverse events, and physician judgement, introducing potential selection bias. Third, MRD was assessed at a sensitivity of 10^{-5}, which is lower than the 10^{-6} and 10^{-7} thresholds used in some recent studies, and PET-CT was not routinely incorporated, potentially resulting in the incomplete capture of low-level residual disease. Fourth, the maintenance strategies were heterogeneous, and patients treated with contemporary anti-CD38 antibody–based quadruplet induction were not included, limiting the generalizability of our findings to current treatment paradigms. Finally, quality-of-life and health-economic outcomes were not systematically assessed; future studies should further examine the long-term impact of discontinuation strategies on patient-reported outcomes and healthcare burden.

In conclusion, our real-world data suggest that maintenance discontinuation is a potential treatment strategy for carefully selected transplant-eligible patients with MM who achieve sustained MRD negativity. HRCA status and the duration of MRD negativity may provide useful information for estimating relapse risk after discontinuation; specifically, the treatment options for patients with high-risk cytogenetic features or relatively short durations of MRD negativity should be considered cautiously. The results of ongoing prospective studies—including DRAMMATIC, RADAR, and FREEDMM—are expected to further define the appropriate patient population, optimal timing, and standardized criteria for MRD-guided discontinuation. For patients who achieve deep and durable responses, individualized adjustment of treatment intensity may be an important direction for the continued evolution of MM management.

Statements and Declarations

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Competing Interests

The authors declare that they have no relevant conflicts of interest to disclose per ICMJE requirements. No commercial relationships, consultancy fees, patent-related benefits, or other financial competing interests exist for any author.

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Data Availability Statement

The data generated in this study are available upon request from the corresponding author.

Ethics Approval

This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (Approval Number: [2025]236) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal guardians before inclusion in the study.

Informed Consent

Written consent was obtained from all patients or their legal guardians, ensuring their voluntary participation in the study. The authors affirm that all patients included in this study provided written consent for the publication of their data and findings in this manuscript. All patient information was anonymized to protect privacy in accordance with ethical guidelines.

Declaration of Generative AI Use

No generative-AI large-language models were used for study design, data analysis, result interpretation, or original manuscript drafting. Minor language polishing was performed using commercial grammar-check software only for readability, with full human review and revision by all authors.

References

Attal M, Lauwers-Cances V, Marit G (2010) Maintenance treatment with lenalidomide after transplantation for myeloma: final analysis of the IFM 2005-02. Blood 116(21):310. https://doi.org/10.1182/blood.V116.21.310.310

Badros A, Foster L, Anderson LD Jr (2025) Daratumumab with lenalidomide as maintenance after transplant in newly diagnosed multiple myeloma: the AURIGA study. Blood 145(3):300–310. https://doi.org/10.1182/blood.2024025746

Costa LJ, Chhabra S, Medvedova E (2023) Minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma (MASTER): final report of the multicentre, single-arm, phase 2 trial. Lancet Haematol 10(11):e890–e901. https://doi.org/10.1016/S2352-3026(23)00236-3

D'Agostino M, Bertuglia G, Rota-Scalabrini D, et al (2024) Predictors of unsustained measurable residual disease negativity in patients with multiple myeloma. Blood 143(7):592–596. https://doi.org/10.1182/blood.2023022080

Derman BA (2023) MRD-guided treatment cessation in multiple myeloma. Lancet Haematol 10(11):e867–e868. https://doi.org/10.1016/S2352-3026(23)00240-5

Derman BA, Major A, Cooperrider J, et al (2024) Discontinuation of maintenance therapy in multiple myeloma guided by multimodal measurable residual disease negativity (MRD2STOP). Blood Cancer J 14(1):170. https://doi.org/10.1038/s41408-024-01156-x

Facon T, Dimopoulos MA, Leleu XP, et al (2024) Isatuximab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 391(17):1597–1609. https://doi.org/10.1056/NEJMoa2400712

Gan X, Li L, Zhang L, Zheng Y, Niu T, Yu Z (2026) Evidence for the monitoring of minimal residual disease dynamics to guide clinical practice in patients with multiple myeloma. Target Oncol 21(2):167–186. https://doi.org/10.1007/s11523-026-01199-z

Giri S, Dhakal B, Callander NS, et al (2025) Optimal MRD-based end point to support response-adapted treatment cessation in newly diagnosed multiple myeloma. Blood 146(6):707–716. https://doi.org/10.1182/blood.2024027674

Goldschmidt H, Mai EK, Dürig J (2020) Response-adapted lenalidomide maintenance in newly diagnosed myeloma: results from the phase III GMMG-MM5 trial. Leukemia 34(7):1853–1865. https://doi.org/10.1038/s41375-020-0724-1

Guerrero C, Puig N, Cedena MT, et al (2024) Predictors of unsustained measurable residual disease negativity in transplant-eligible patients with multiple myeloma. Blood 143(7):597–603. https://doi.org/10.1182/blood.2023022083

Holstein SA, Jung SH, Richardson PG (2017) Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. Lancet Haematol 4(9):e431–e442. https://doi.org/10.1016/S2352-3026(17)30140-0

Jackson GH, Davies FE, Pawlyn C, et al (2019) Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 20(1):57–73. https://doi.org/10.1016/S1470-2045(18)30687-9

Kaiser MF, Hall A, Phillip R (2024) Extended intensified consolidation and maintenance improve ultra high-risk multiple myeloma patient outcome: long-term follow-up of the UKMRA OPTIMUM/MUKnine trial. Blood 144(Suppl 1):3354. https://doi.org/10.1182/blood-2024-201086

Leypoldt LB, Ginde VR, Besemer B (2025) Isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) for high-risk (HR) newly diagnosed multiple myeloma (NDMM): first-time report of the full cohort of transplant-eligible (TE) patients in the GMMG-CONCEPT trial. J Clin Oncol 43(16 Suppl):7509. https://doi.org/10.1200/JCO.2025.43.16_suppl.7509

McCarthy PL, Owzar K, Hofmeister CC (2012) Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 366(19):1770–1781. https://doi.org/10.1056/NEJMoa1114083

Meseha M, Hoffman J, Kazandjian D, Landgren O, Diamond B (2024) Minimal residual disease-adapted therapy in multiple myeloma: current evidence and opinions. Curr Oncol Rep 26(6):679–690. https://doi.org/10.1007/s11912-024-01537-2

Paiva B, San-Miguel JF (2025) Myeloma: a sky full of MRD stars. Blood 146(6):649–650. https://doi.org/10.1182/blood.2025029160

Paiva B, Shi Q, Puig N, et al (2025) Opportunities and challenges for MRD assessment in the clinical management of multiple myeloma. Nat Rev Clin Oncol 22(6):424–438. https://doi.org/10.1038/s41571-025-01017-x

Perrot A, Lauwers-Cances V, Cazaubiel T (2020) Early versus late autologous stem cell transplant in newly diagnosed multiple myeloma: long-term follow-up analysis of the IFM 2009 trial. Blood 136(Suppl 1):39. https://doi.org/10.1182/blood-2020-134538

Perrot A, Lambert J, Hulin C, et al (2025) Measurable residual disease-guided therapy in newly diagnosed myeloma. N Engl J Med 393(5):425–437. https://doi.org/10.1056/NEJMoa2505133

Rajkumar SV, Dimopoulos MA, Palumbo A, et al (2014) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 15(12):e538–e548. https://doi.org/10.1016/S1470-2045(14)70442-5

Richardson PG, Jacobus SJ, Weller EA (2022) Triplet therapy, transplantation, and maintenance until progression in myeloma. N Engl J Med 387(2):132–147. https://doi.org/10.1056/NEJMoa2204925

Rodríguez-Otero P, Moreau P, Dimopoulos MA (2024) Daratumumab (DARA) + bortezomib/lenalidomide/dexamethasone (VRd) in transplant-eligible (TE) patients (pts) with newly diagnosed multiple myeloma (NDMM): analysis of minimal residual disease (MRD) in the PERSEUS trial. J Clin Oncol 42(16 Suppl):7502. https://doi.org/10.1200/JCO.2024.42.16_suppl.7502

Sato S, Sawazaki E, Tsunoda S, Kamata W, Togano T, Tamai Y (2025) Retrospective analysis of treatment discontinuation in minimal residual disease negative multiple myeloma. Int J Hematol 122(2):217–223. https://doi.org/10.1007/s12185-025-03966-6

Sato K, Suzuki K, Sugita S, et al (2026) Treatment discontinuation after achieving MRD negativity in multiple myeloma in the Pre-BCMA era: a prospective, single-centre study. eJHaem 7(2):e70281. https://doi.org/10.1002/jha2.70281

Sneider AP, Derman BA (2025) The role of maintenance therapy and its cessation in patients with multiple myeloma. Leuk Lymphoma 66(13):2426–2436. https://doi.org/10.1080/10428194.2025.2551785

Sonneveld P, Dimopoulos MA, Boccadoro M (2024) Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 390(4):301–313. https://doi.org/10.1056/NEJMoa2312054

Terpos E, Malandrakis P, Ntanasis-Stathopoulos I, et al (2025) Sustained bone marrow and imaging MRD negativity for 3 years drives discontinuation of maintenance post-ASCT in myeloma. Blood 145(20):2353–2360. https://doi.org/10.1182/blood.2024027686

Touzeau C, Perrot A, Hulin C (2022) Daratumumab carfilzomib lenalidomide and dexamethasone as induction therapy in high-risk, transplant-eligible patients with newly diagnosed myeloma: results of the phase 2 study IFM 2018-04. J Clin Oncol 40(16 Suppl):8002. https://doi.org/10.1200/JCO.2022.40.16_suppl.8002

van de Donk N, Pawlyn C, Yong KL (2021) Multiple myeloma. Lancet 397(10272):410–427. https://doi.org/10.1016/S0140-6736(21)00135-5

Voorhees PM, Kaufman JL, Laubach J, et al (2020) Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood 136(8):936–945. https://doi.org/10.1182/blood.2020005288