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REVIEW

The Rapidly Evolving Treatment Landscape in Newly Diagnosed Multiple Myeloma: Current Status and Future Directions

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Over the past two decades, significant progress has been made in the management of multiple myeloma (MM), leading to the development of novel therapeutic approaches and treatment regimens to improve patient outcomes. In patients with newly diagnosed MM (NDMM), the introduction of anti-CD38 monoclonal antibodies daratumumab and isatuximab has significantly extended patient survival while maintaining a manageable toxicity profile and building upon the success of highly active triplet combinations incorporating immunomodulatory drugs, proteasome inhibitors and dexamethasone. Treatment strategies based on the assessment of minimal residual disease (MRD) negativity, a strong prognostic marker for durable responses, allow for improved decision making in MM management. Active ongoing research aims to assess how novel therapies may improve outcomes in both frontline and maintenance settings. This review article discusses recent advances in NDMM therapy, with a focus on quadruplet versus triplet anti-CD38 mAb-based regimens and MRD-driven approaches, as well as emerging alternative therapeutic strategies, including transplant-sparing approaches to meaningfully improve patient outcome. Ongoing trials are also outlined, including the data presented at the 65th American Society of Hematology (ASH) Annual Meeting & Exposition, the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting, the 2024 European Hematology Association (EHA) Congress and the 21st International Myeloma Society (IMS) Annual Meeting 2024.

PEER REVIEWED ARTICLE

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Introduction

Multiple myeloma (MM) is a hematological malignancy with an estimated incidence in Europe of 4.5–6.0/100,000/year.[1] In Switzerland, an estimated 570 individuals are diagnosed with MM each year and approximately 440 will die of this disease. Based on data collected between 1991 and 2015, there has been a general trend towards increased survival among patients in Switzerland, in particular among patients aged <65 years, and similar patterns of improvement in outcome have been seen globally, especially in the USA.[2,3]

MM is caused by clonal proliferation of plasma cells in the bone marrow. Its clinical symptoms include osteolytic bone lesions, bone pain, hypercalcemia, renal insufficiency, suppressed hematopoietic function, reduced polyclonal immunoglobulin production and increased bone marrow angiogenesis.[1,4,5] The introduction of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) has improved response rates, quality of life and survival of MM patients.[6] Over the past two decades, significant progress has been made in the management of MM, resulting in longer and more profound remissions, as well as extended survival periods. Current treatment options for MM include multiple drug classes, among them corticosteroids (prednisone and dexamethasone), proteasome inhibitors (PIs) such as bortezomib, carfilzomib and ixazomib, and immunomodulatory drugs (IMiDs) including lenalidomide, thalidomide and pomalidomide. Furthermore, immunotherapeutic approaches have demonstrated efficacy in the treatment of MM. These include monoclonal antibodies (mAbs), antibody-drug conjugates (ADC), bispecifics and chimeric antigen receptor (CAR) T-cells that target various plasma cell antigens, such as B-cell maturation antigen (BCMA), CD38, the Fc receptor-like protein 5 (FCRL5) and G protein-coupled receptor, class C group 5 member D (GPRC5D).[1,7-9] Despite these achievements, MM remains an incurable disease that eventually relapses as tumor cells develop refractoriness due to cytogenetics and clonal changes, indicating the need for novel treatment strategies for relapsed/refractory disease, as well as in the frontline setting to induce long-term remission.[1,10-12]

Anti-CD38 monoclonal antibodies in MM therapy

Anti-CD38 mAbs target human CD38 antigen, a transmembrane glycoprotein that mediates signaling events, adhesion and enzymatic activity.[13] CD38 is expressed on hematopoietic cells, T cells, B cells and myeloid-derived suppressor cells. Its surface overexpression is associated with compromised immune surveillance in various malignancies, including acute leukemia, chronic lymphocytic leukemia, lymphomas and MM. The development of mAbs against CD38 has transformed MM treatment owing to their anti-tumor efficacy and manageable safety profile. CD38-targeted therapies eliminate tumor cells *via* antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), direct apoptosis, enzymatic inhibition and immunomodulation (**Figure 1**).[14] Two anti-CD38 mAbs, daratumumab and isatuximab, are currently approved for the treatment of MM in the US.[15] These antibodies exhibit both similarities and dissimilarities in their mechanisms of action, which are likely attributable to their distinct, non-overlapping binding sites on the CD38 molecule.[16] Isatuximab saturates the CD38 membrane and can be internalized, leading to membrane dynamics different from that of daratumumab.[17] Both daratumumab and isatuximab can inhibit or eliminate malignant cells by CDC, ADCC, ADCP and indirect apoptosis via Fc gamma receptor-mediated cross-linking, whereas isatuximab can also directly stimulate apoptosis. Both agents have immunomodulatory functions, possibly contributing to antitumor responses.[15,18,19] Anti-CD38 mAbs have proven to be useful when combined with chemotherapy and ASCT, with a tolerable toxicity profile. Infusion-related reactions are the primary adverse events (AEs) associated with daratumumab and isatuximab, although these events are infrequent following the second infusion.[20]

Current treatment recommendations in NDMM

Treatment options of newly diagnosed MM (NDMM) vary depending on many factors, including patient age, frailty, comorbidities, eligibility for ASCT, as well as the presence of high-risk cytogenetic features.[21,22] High-risk chromosomal abnormalities predicting poor response in MM include deletion of chromosome arm 17p (del(17p)) and/or *TP53* mutation, translocation t(4;14), t(14;16) or t(14;20) co-occurring with 1q and/or del(1p32), monoallelic del(1p32) along with +1q or biallelic del(1p32).[23-25] Other risk factors are clinical biomarkers and features such as International Staging System (ISS) stage III, high β2 microglobulin levels (>5.5 mg/dL) with normal creatinine (<1.2 mg/dL), high serum lactate dehydrogenase, circulating plasma cells, central nervous system involvement, plasmablastic morphology and renal dysfunction.[22,25,26] Minimal residual disease (MRD) negativity is a strong prognostic marker for durable responses, longer progression-free survival (PFS) and overall survival (OS), regardless of cytogenetic risk.[27] Historically, high-risk patients constituted a small part of

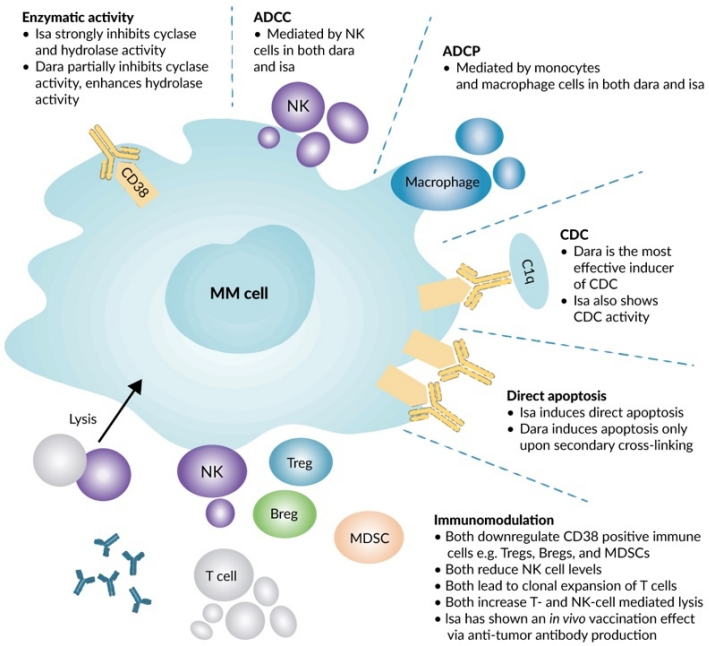

Figure 1. Anti-CD38 agents: Mechanism of action.

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; Breg, regulatory B cell; CDC, complement-dependent cytotoxicity; Dara, daratumumab; Isa, isatuximab; MDSC, myeloid-derived suppressor cell; NK, natural killer; Treg, regulatory T cell. Adapted from Bisht et al. 2023.[14]

phase III clinical trial cohorts (approximately 15%); thus, available evidence for treating this population is limited. ASCT eligibility plays a large role when determining treatment options for patients with high-risk NDMM.[21,28]

Traditionally, induction therapy consists of triplet regimens, based on a combination of an IMiD, PI and corticosteroid.[29] Following evidence from the phase III CASSIOPEIA trial,[30] more recent quadruplet regimens add anti-CD38 mAbs to the triplet backbone (**Figure 2**).[1,21] The European Society for Medical Oncology (ESMO) recommendations for fit NDMM patients aged <70 years, without comorbidities, include induction therapy followed by high-dose therapy (such as melphalan)/ASCT and lenalidomide maintenance.[1] While the European Medicines Agency (EMA) has approved lenalidomide for maintenance therapy post-ASCT for all MM patients until progression, bortezomib and ixazomib have not yet received approval.[1] In patients that are transplant-ineligible, there are three standards of care: bortezomib plus lenalidomide and dexamethasone (RVd), daratumumab plus bortezomib, melphalan and prednisone (D-VMP) or daratumumab plus lenalidomide and dexamethasone (D-Rd). Although quadruplet therapy incorporating anti-CD38 therapies has promising results compared with triplet therapy, increased rates of hematologic AEs and infections are common.[31-34]

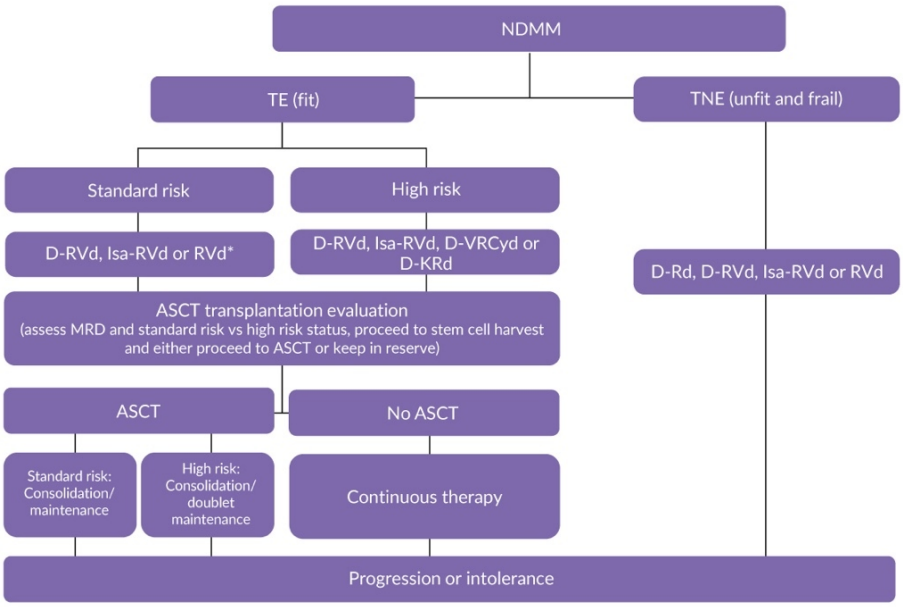

Figure 2. Treatment algorithm for patients with newly diagnosed multiple myeloma (NDMM).

ASCT, autologous stem cell transplantation; D-Rd, daratumumab plus lenalidomide and dexamethasone; D-KRd, daratumumab plus carfilzomib, lenalidomide and dexamethasone; D-RVCyd, daratumumab plus lenalidomide, bortezomib, cyclophosphamide and dexamethasone; D-RVd, daratumumab plus lenalidomide, bortezomib and dexamethasone; Isa-RVd, isatuximab plus lenalidomide, bortezomib and dexamethasone; MRD, minimal residual disease; RVd, bortezomib plus lenalidomide and dexamethasone; TE, transplant eligible; TNE, transplant non-eligible. *The use of RVd alone in the standard-risk group can only be justified if mAbs are not available.

The next sections discuss recent advances in NDMM therapy, with a focus on anti-CD38 mAb therapy and MRD-driven approaches, and highlight some emerging alternative therapies and ongoing trials, including the data presented at the 65th American Society of Hematology (ASH) Annual Meeting & Exposition, the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting, the 2024 European Hematology Association (EHA) Congress and the 21st International Myeloma Society (IMS) Annual Meeting 2024.

Recent clinical research in patients with NDMM

Daratumumab-based triplet therapy in transplant-ineligible patients

In the phase III MAIA trial, the benefit of D-Rd versus Rd alone was analyzed in patients (n=737) with ASCT-ineligible NDMM.[35] The initial findings showed a benefit for D-Rd versus Rd on the 30-month PFS rate (70.6% vs 55.6%; HR: 0.56 [95% CI: 0.43–0.73]; p<0.001). Patients who received daratumumab also displayed a higher response (CR) rate (47.6% vs 24.9%; p<0.001). An updated analysis showed that patients continued to benefit from D-Rd versus Rd (median PFS: 61.9 vs 34.4 months [HR: 0.55]; median OS: not reached vs 64.1 months [HR: 0.65]).[36] The most common

grade 3–4 AEs were neutropenia, anemia, lymphopenia and pneumonia (50.0% vs 35.3%, 11.8% vs 19.7%, 15.1% vs 10.7% and 13.7% vs 7.9% with D-Rd vs Rd, respectively). Exploratory analyses supported the benefit of D-Rd versus Rd on PFS, OS, overall response rate (ORR), and MRD negativity across several high-risk subgroups, including older and frail patients and those with renal insufficiency, extramedullary plasmacytomas, and high cytogenetic risk.[32,37,38] In summary, MAIA demonstrated a substantial gain in PFS and OS with D-Rd positioning the regimen as the new standard of care in this setting.

Daratumumab-based quadruplet induction/consolidation therapy plus ASCT

The phase III PERSEUS trial reported a benefit of the quadruplet regimen of subcutaneous daratumumab plus RVd (D-RVd) versus triplet RVd regimen in transplant-eligible patients with NDMM (n=709).[39,40] Patients in Arm 1 received D-RVd during induction, followed by high-dose therapy plus ASCT, consolidation with D-RVd and maintenance with daratumumab plus lenalidomide (D-R). Arm 2 received the same regimen but without daratumumab. After two years of maintenance therapy, patients with sustained MRD negativity for at least 12 months could discontinue daratumumab. The primary endpoint was PFS.

At four years, there was a statistically significant improvement in PFS with D-RVd versus RVd (84.3% vs 67.7%; HR: 0.42 [95% CI: 0.30–0.59]; p<0.0001) (**Figure 3**).[39] The PFS benefit was consistent across subgroups, including patients with ISS stage III disease and high-risk cytogenetics.

In both treatment arms, responses and rates of MRD negativity deepened over time, with a higher rate of improvement in patients receiving D-RVd.[41] In the D-RVd arm, the rates of CR or better were 22.5% at the end of induction, 27.9% at the end of ASCT, 44.5% at the end of consolidation and 87.9% overall; these rates were 21.2%, 23.4%, 34.7% and 70.1% in the RVd arm, respectively. Further data showed that 47.3% of patients receiving D-RVd had MRD negativity at a 10^{-6} sensitivity for at least 12 months compared with 18.6% of patients receiving RVd. At a 10^{-5} sensitivity, these rates were 64.8% and 29.7%, respectively. Sustained MRD negativity at a 10^{-6} sensitivity for at least 18 months was observed in 42.0% of patients receiving D-RVd compared with 15.0% of those receiving RVd; these rates were 59.4% and 25.1% at a 10^{-5} sensitivity. Sustained MRD negativity rates were improved with D-RVd plus D-R versus RVd plus R across prespecified subgroups, including patients with high-risk disease. Among patients who were positive at 10^{-6} sensitivity, 56.7% in the D-RVd arm and 25.2% in the RVd arm became MRD-negative during maintenance (p<0.0001). At 10^{-5} sensitivity, 60.2% of patients treated with D-RVd who were MRD-positive became MRD-negative compared with 40.5% of patients treated with RVd (p=0.0049). In

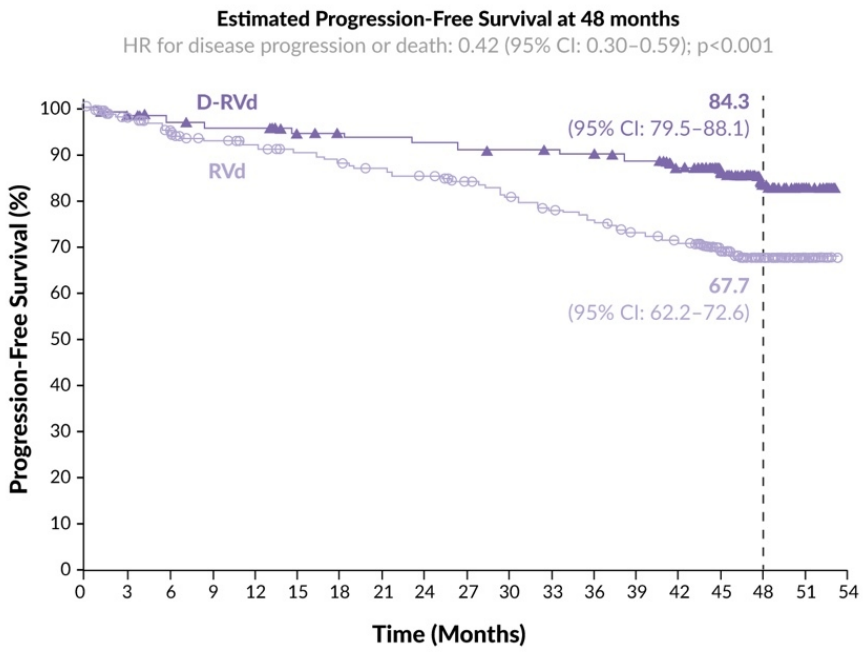

Figure 3. PERSEUS: Improved progression-free survival (PFS) with daratumumab plus lenalidomide, bortezomib and dexamethasone (D-RVd) versus RVd as induction/consolidation therapy plus autologous stem cell transplantation (ASCT).

Adapted from Sonneveld et al. 2024.[39]

terms of safety, the most common grade 3–4 AEs were neutropenia and thrombocytopenia (62.1% vs 51.0% and 29.1% vs 17.3% with D-RVd vs RVd respectively).

Similar to PERSEUS, the phase II GRIFFIN study investigated D-RVd versus RVd in patients with transplant-eligible NDMM (n=104).[42] This final analysis demonstrated that D-RVd improved rates of stringent CR (sCR, 67% vs 48%) and 4-year PFS (87.2% vs 70.0%) versus RVd, with a hazard ratio (HR) of 0.45 ([95% CI: 0.21–0.95]; p=0.032) for the risk of disease progression or death. The median OS was not reached in either arm, with a 4-year OS rate of 92.7% with D-RVd versus 92.2% with RVd. Grade 3–4 treatment-emergent AEs (TRAEs) in the D-RVd versus RVd arms included neutropenia (46% vs 23%), lymphopenia (23% vs 23%), leukopenia (17% vs 8%) and thrombocytopenia (16% vs 9%). These data further support the use of quadruplet D-RVd regimen in this patient population.

In the single-arm, phase II MASTER study, 123 patients with NDMM and high-risk cytogenetics received induction therapy with daratumumab plus carfilzomib, lenalidomide and dexamethasone (D-KRd), followed by ASCT and consolidation therapy.[43] The MRD status was used to modulate treatment duration and cessation: patients who remained MRD-negative following two consecutive tests were moved to treatment-free surveillance, while those who were MRD-positive after consolidation received lenalidomide maintenance therapy. Patients with ≤1 high-risk cytogenetic

abnormalities (HRCA) performed better on D-KRd than those with ≥2 abnormalities (3-year PFS for 0 vs 1 vs ≥2 HRCA's: 88.4% vs 78.9% vs 50.0%; 3-year OS: 94% vs 92% vs 75%). MRD-adapted therapy reduced the effect of MRD positivity on PFS and OS by the cessation of induction. A subgroup analysis showed that the 3-year PFS and OS benefits with D-KRd were similar in younger and older patients (<70 vs ≥70 years).[44] These data show a strong clinical benefit with D-KRd plus ASCT in patients with (ultra-)high-risk cytogenetics and highlight that MRD status can be used to identify when to cease active treatment in the high-risk group. For ultra-high-risk patients, however, decisions regarding treatment deintensification should not be made solely on the basis of achieving MRD goals.

IFM-2018-04 is a phase II study that confirmed the feasibility of an intensive treatment program in transplant-eligible patients (n=50) with NDMM and high-risk cytogenetic abnormalities.[45] Patients received D-KRd induction, stem cell mobilization/collection, ASCT 1, consolidation, ASCT 2 and two years of daratumumab plus lenalidomide maintenance. A recently reported final analysis demonstrated that the study met its primary endpoint, with 72% of patients completing a second transplant,[45] as well as high rates of sCR/CR (81%) and MRD negativity (94%). At the median follow-up of 32-months, the 30-month PFS and OS rates were 80% and 91%, respectively. In summary, the study confirmed the feasibility of quadruplet induction/consolidation with tandem ASCT in high-risk patients.

Daratumumab-based quadruplet induction without ASCT

The non-randomized MANHATTAN trial evaluated D-KRd in patients with NDMM (n=41) without high-dose melphalan chemotherapy or ASCT.[46] The primary endpoint was MRD negativity rate. This landmark study achieved high rates of MRD negativity (71%), with 1-year PFS and OS rates of 98% and 100%, respectively. These data provide compelling evidence for further investigation of quadruplet therapies without ASCT.

In the phase III GEM2017FIT trial, fit patients with transplant-ineligible NDMM (n=462) were randomized to receive induction therapy with bortezomib, melphalan and prednisone (VMP) followed by Rd (VMP-Rd, n=154), KRd (n=154) or D-KRd (n=153), followed by daratumumab plus lenalidomide consolidation and maintenance.[47] The trial met its primary endpoint, with the MRD negativity rates after induction being significantly higher with either KRd (75%; p<0.0001) or D-KRd (84%; p<0.0001) compared with the standard VMP-Rd (33%). Longer PFS was reported for both KRd alone (83%) and D-KRd (79%) compared with the VMP-Rd (73%). ORR and median OS were similar across treatment arms; however, sCR/CR rates were significantly lower for patients in the VMP-Rd arm compared with those in the KRd-alone (59%; p<0.0001) or D-KRd (61%;

p<0.0001) arms. The rates of early discontinuation were similar in all arms. These results support the use of the D-KRd quadruplet therapy in fit, older patients.

The recently reported data from the multicenter, randomized, open-label, phase III CEPHEUS study demonstrated improved MRD negativity rates, complete response rates and PFS with D-RVd compared with RVd in NDMM patients (n=396) for whom ASCT was not planned as initial therapy (transplant ineligible or deferred).[48] At a median follow-up of 58.7 months, the study met its primary endpoint, with an overall MRD-negativity rate (at 10^{-5} sensitivity) of 60.9% with D-RVd versus 39.4% with RVd (odds ratio [OR]: 2.37 [95% CI: 1.58–3.55]; p<0.0001). The proportion of patients achieving sustained MRD negativity of ≥12 months was 48.7% for D-RVd versus 26.3% for RVd (p<0.0001). The median PFS was not reached with D-RVd versus 52.6 months for RVd (HR: 0.57 [95% CI: 0.41–0.79]; p<0.0005), corresponding to a 43% reduction in the risk of progression or death with D-RVd.

Isatuximab-based quadruplet induction/consolidation therapy plus ASCT

The phase III IsKia trial is the first to compare the efficacy and safety of a triplet KRd regimen versus quadruplet isatuximab plus KRd (Isa-KRd) in patients with transplant-eligible NDMM (n=302).[49] Patients received induction, mobilization, ASCT, consolidation and lenalidomide maintenance therapy. The primary endpoint was the post-consolidation MRD negativity rate. The data presented at ASH 2023 showed that the post-consolidation MRD negativity rate was higher with Isa-KRd versus KRd at both MRD sensitivity thresholds ($<10^{-5}$, 77% vs 67%; p=0.049 [achieving primary endpoint]; $<10^{-6}$, 67% vs 48%; p<0.001).[50] The subgroup of patients with high-risk cytogenetics showed the greatest improvement with Isa-KRd versus KRd (77% vs 27%) (**Figure 4**). Common grade 3–4 hematological AEs were neutropenia (37% vs 22%) and thrombocytopenia (15% vs 17%). In summary, data from the IsKia trial demonstrated that Isa-KRd is promising, particularly for patients with high-risk cytogenetics. However, with similar 1-year PFS rates in both arms, mature PFS data are needed to estimate patient benefits.

The open-label phase III GMMG-HD7 trial evaluated the benefit of induction therapy with isatuximab plus RVd (Isa-RVd) versus RVd alone in transplant-eligible patients with NDMM (n=660).[33] The primary endpoint was MRD negativity in the intention-to-treat (ITT) population. The results showed that patients responded better to Isa-RVd compared with RVd, with higher rates of post-induction MRD negativity (50.1% vs 35.6%), very good partial response (VGPR) rates (53.1% vs 38.9%) and ORR (90.0% vs 83.6%). In a recent interim analysis, Isa-RVd continued to show a significant improvement in MRD negativity rates after intensification therapy (66.2%

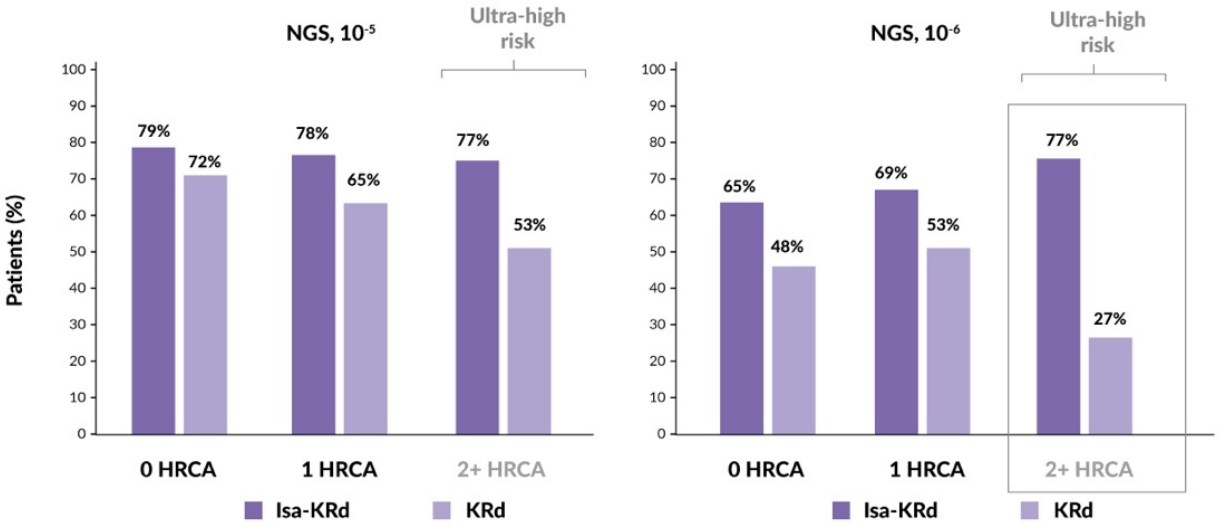

Figure 4. IsKia: Isatuximab plus carfilzomib, lenalidomide and dexamethasone (Isa-KRd) increases post-consolidation minimal residual disease (MRD) negativity rates compared with KRd, especially in ultra-high-risk patients.

HRCA, high-risk cytogenetic abnormality; NGS, next-generation sequencing. Adapted from Gay et al. 2023.[49]

vs 47.7% with RVd; OR: 2.13 [95% CI: 1.56–2.92]; p<0.001).[51] Treatment with Isa-Rd also led to significantly improved rates of MRD negativity/VGPR (63.4% vs 43.8% with RVd; p<0.001) and MRD negativity/CR or better (38.1% vs 25.8%; p<0.001). Upon completing intensification, 72.0% of patients in the Isa-RVd arm and 56.5% of patients in the RVd arm achieved MRD negativity (OR: 1.98 [95% CI: 1.39–2.85]; p<0.001). These data are promising and support the incorporation of isatuximab into induction therapy for transplant-eligible patients with NDMM.

The small phase II SKylaRk study investigated Isa-KRd in 50 patients with transplant-eligible NDMM.[52,53] Patients received induction with isa-KRd, followed by the option of upfront or deferred ASCT, Isa-KRd consolidation and maintenance with lenalidomide (standard-risk cytogenetics) or isatuximab plus carfilzomib and lenalidomide (high-risk cytogenetics). As first reported at ASH 2023, and potentially this year, patients experienced deep and durable responses after four treatment cycles, with an ORR of 100%, a VGPR rate of 89% and a CR rate of 36%, of which 43% were MRD-negative. After six to eight cycles, the ORR, CR and VGPR or better were 100%, 64% and 96%, respectively, with 66% of patients being MRD-negative. The 24-month PFS and OS rates were 91.3% and 95.8%, respectively. Grade 3–4 AEs occurring in at least two patients included neutropenia (26%), elevated alanine aminotransferase (12%), acute kidney injury (4%) and thrombocytopenia (6%). These data support the Isa-KRd regimen in this population, including transplant-ineligible patients with NDMM.

The phase II GMMG-CONCEPT trial investigated Isa-KRd in 125 transplant-eligible and ineligible patients with high-risk NDMM.[54] Patients received Isa-KRd induction/consolidation and Isa-carfilzomib-lenalidomide maintenance; transplant-eligible patients received high-dose melphalan, whereas ineligible patients received additional post-induction Isa-KRd. This trial met its primary endpoint of MRD negativity at the end of consolidation, with greater MRD negativity rates in transplant-eligible versus transplant-ineligible patients (67.7% vs 54.2%). In total, 81.2% of patients treated with Isa-KRd achieved MRD-negative status. Isa-KRd led to durable responses, with 62.6% of patients remaining MRD-negative after ≥1 year. The median PFS was not reached in either treatment arm. In summary, the study demonstrated impressive results in both subgroups, supporting the use of Isa-KRd as a promising therapy in patients with limited treatment options.

Isatuximab-based quadruplet therapy for transplant-ineligible patients

The first results were recently reported from the phase III IMROZ trial, which aimed to assess the efficacy and safety of Isa-RVd versus RVd in transplant-ineligible patients with NDMM.[55,56] In this study, 446 patients (aged ≤80 years) underwent 3:2 randomization to receive either four 6-week induction cycles of Isa-RVd or RVd, followed by 4-week cycles of maintenance Isa-Rd or Rd. At a median follow-up of 59.7 months, the study met its primary endpoint of PFS, with a median PFS of not reached with the isatuximab-containing regimen versus 54.34 months with RVd and 60-month PFS rates of 63.2% versus 45.2%, respectively (HR: 0.596 [95% CI: 0.406–0.876]; p=0.0005) (**Figure 5**). PFS benefits with Isa-RVd were observed in most patient subgroups, including difficult-to-treat populations with negative prognostic factors, such as patients aged ≥75 years and those with extramedullary disease. Treatment with Isa-RVd followed by Isa-Rd resulted in deep response rates, with a significant improvement in MRD negativity rates. Three-quarters of patients receiving Isa-RVd achieved a CR or better compared with 64.1% of patients receiving RVd. VGPR or better was reported in 89.1% of patients with Isa-RVd versus 82.9% of patients with RVd. The MRD negativity rates in the ITT population were 58.1% with Isa-RVd versus 43.6% with RVd (OR: 1.791) and 55.5% versus 40.9% among patients who achieved CR (OR: 1.803), respectively. The rates of sustained MRD negativity for ≥12 months were 46.8% in the Isa-RVd arm versus 24.3% in the RVd arm (OR: 2.729). At the data cut-off, although the OS data were still immature, there was a favorable trend toward improved OS with Isa-RVd, showing a 22.4% risk reduction compared with RVd (HR: 0.776 [95% CI: 0.407–1.480]) and 60-month OS rates of 72.3% versus 66.3%, respectively. Regarding safety, Isa-RVd was well tolerated, with a safety profile being consistent with that of each agent.

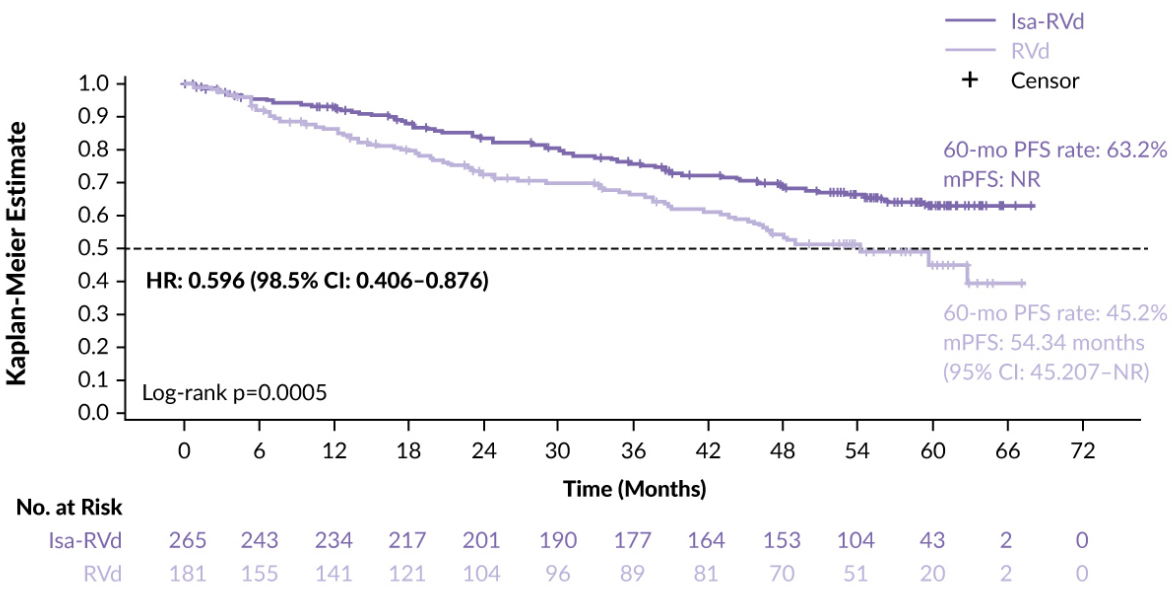

Figure 5. IMROZ: Progression-free survival (PFS) in transplant-ineligible patients treated with isatuximab plus lenalidomide, bortezomib and dexamethasone (Isa-RVd) versus RVd.

mo, month; mPFS, median PFS; NR, not reached. Adapted from Facon et al. 2024.[55]

The combination of isatuximab and RVd was also investigated in the phase III BENEFIT trial in transplant-ineligible patients with NDMM.[57-59] This study enrolled 270 non-frail patients (aged 65–79 years) to receive either Isa-RVd (n=135) or Isa-Rd (n=135) for 12 cycles, followed by Isa-VR or Isa-R, respectively, for six cycles and maintenance therapy with Isa-R in both treatment arms. At 18 months, MRD negativity rates at 10^{-5} were significantly higher among patients receiving the quadruplet versus triplet regimens (53% vs 26%; OR: 3.16 [95% CI: 1.89–5.28]; p<0.0001). The 18-month MRD negativity rates at 10^{-6} were 36% with Isa-RVd versus 17% with Isa-Rd (OR: 2.74 [95% CI: 1.54–4.87]; p<0.0006). Higher MRD negativity rates in the Isa-RVd were also observed at 12 months at both 10^{-5} and 10^{-6} sensitivity. Isa-RVd was further associated with significantly improving the MRD negativity/CR rates at 12 and 18 months at both 10^{-5} and 10^{-6}. At 18 months, patients receiving Isa-RVd versus IsaRd also had significantly improved rates of CR or better (58% vs 31%; OR: 2.97 [95% CI: 2–5]; p< 0.0001) and VGPR or better (82% vs 70%; p< 0.0001). At a median follow-up of 23.5 months, PFS and OS data were still immature; the estimated 24-month PFS and OS rates were 85.2% and 91.1% for Isa-RVd versus 80.0% and 91.5% for Isa-Rd, respectively.

A large phase IB/II NCT02513186 study evaluated safety, efficacy and pharmacokinetics of Isa-RVd and isatuximab in combination with bortezomib, cyclophosphamide and dexamethasone (Isa-VCd) in patients with NDMM who were transplant-ineligible or without intent for immediate transplant.[60,61] Overall, 73 patients received Isa-RVd induction, followed

by Isa-Rd maintenance. In the efficacy population (n=71), the ORR was 98.6%, with sCR/CR achieved in 56.3% and MRD negativity in 50.7% of patients.[45] Grade ≥3 TRAEs occurred in 79.5% of patients. The Isa-VCd cohort included 17 transplant-ineligible NDMM patients.[61] No dose-limiting toxicities were reported in the dose escalation phase, and the maximum tolerated dose was not reached. Nine additional patients were treated with Isa-VCd during the dose expansion phase. The ORR was 93.3% and the rates of VGPR or better, sCR/CR and MRD negativity were 80.0%, 66.6% and 53.5%, respectively. The median PFS was 63.3 months, and the 5-year OS rate was 79%.

MRD-adapted approaches with quadruplet therapy

The phase III MIDAS trial recruited 792 patients eligible for ASCT to assess the benefit of high-dose melphalan plus ASCT following Isa-KRd induction in NDMM.[62] Post-induction, low-risk (MRD-negative) patients received six additional cycles of Isa-KRd or high-dose melphalan plus ASCT, followed by two cycles of Isa-KRd. High-risk (MRD-positive) patients were randomized to receive high-dose melphalan plus ASCT, followed by two cycles of Isa-KRd or tandem high-dose melphalan plus ASCT. Primary data for this trial are yet to be released.

Following the success of the MANHATTAN trial, the phase III ADVANCE trial was designed to confirm the benefits of D-KRd compared with KRd.[63] Patients will receive D-KRd or KRd, high-dose melphalan plus ASCT (if MRD-positive after eight cycles), followed by lenalidomide maintenance. MRD negativity is the primary endpoint and secondary endpoints include PFS, event-free survival (EFS), sustained MRD negativity, OS and correlative assays. Among the unique features of this study are the full integration of whole-genome sequencing and single-cell sequencing data. More than 57% of the planned patients were recruited, and the initial data confirmed those of the MANHATTAN trial.

Increasing rationale for deferred ASCT in NDMM

While high-dose melphalan plus ASCT remains the standard-of-care treatment approach for eligible patients with NDMM, based on prolonged PFS and high rates of MRD negativity, these gains have not been mirrored in OS.[64] Consequently, there is an increasing rationale and trend, particularly in US clinical practice, to postpone upfront ASCT in selected eligible patients, thereby reducing the initial treatment burden and associated toxicities and reserving ASCT for subsequent salvage therapy as well as reducing later additional complications such as secondary malignancies.[65] Sustained MRD negativity status may be a good surrogate marker for determining whether ASCT should be deferred, as it is predictive of treatment response.[66]

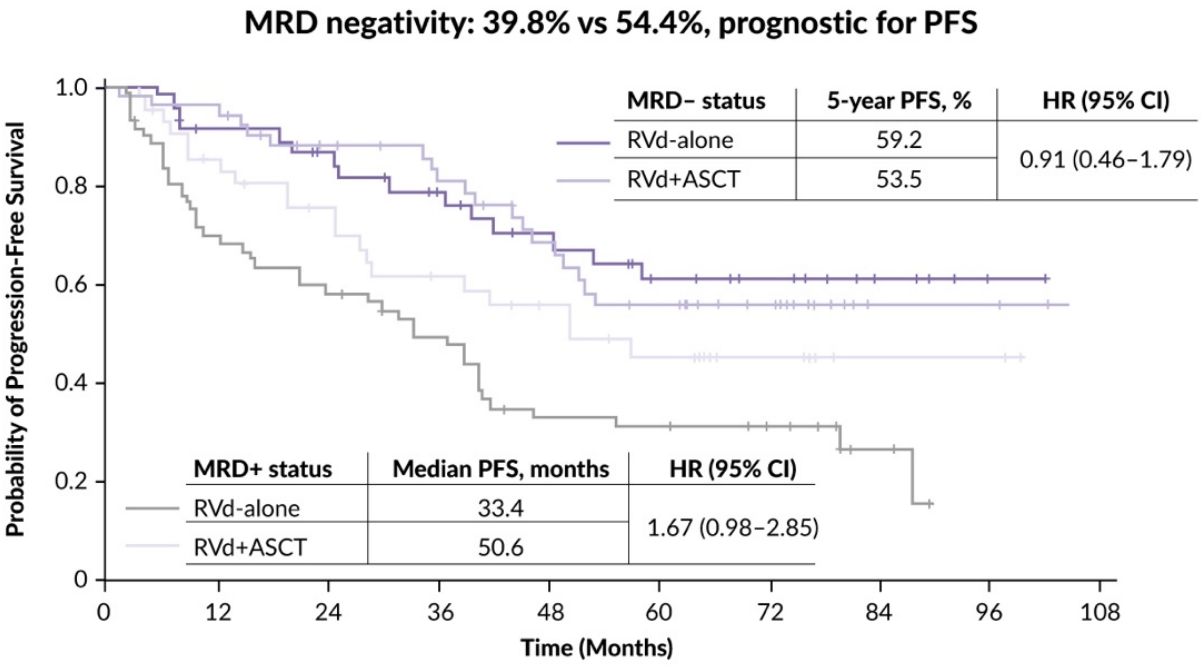

Figure 6. DETERMINATION: Minimal residual disease (MRD) negativity status is prognostic for progression-free survival (PFS) benefit.

ASCT, autologous stem cell transplantation; RVd, lenalidomide, bortezomib and dexamethasone. Adapted from Richardson et al. 2022.[70]

The phase III DETERMINATION trial assessed the benefit of RVd-alone compared with RVd plus ASCT in patients with NDMM (n=722).[67,68] Patients received RVd induction, stem cell mobilization, RVd or ASCT, RVd consolidation and lenalidomide maintenance. The primary endpoint was PFS. RVd plus ASCT was associated with longer median PFS than RVd-alone (67.5 months vs 46.2 months), although no OS benefit was observed despite mature follow-up at a median of 72 months. Moreover, only 28% of the transplant delayed or deferred groups underwent ACST, with 72% having received next-generation novel therapies, including mAbs, at relapse. Stratification of the 5-year PFS rates from DETERMINATION according to MRD status highlights the strong value of this biomarker for predicting patient benefit with triplet therapy alone (**Figure 6**). In a subgroup analysis, African American (AA) patients were more likely to achieve an sCR/CR with RVd alone versus RVd plus ASCT than white patients.[69] AA patients had greater prolongation of PFS with RVd alone, while RVd plus ASCT was more effective in white patients. A high body-mass index in AA patients was associated with greater benefit from RVd versus RVd plus ASCT, and Duffy-null status may play a role in pathobiology. The 5-year OS rate remained similar regardless of race and was enough at approximately 80%.

Maintenance therapy in patients with NDMM

Although significant progress has been made in MM treatment, the majority of patients eventually experience a relapse. Maintenance therapy with lenalidomide has become the standard of care following ASCT, as it has demonstrated the capacity to extend and enhance treatment responses.[71] Several studies evaluated the efficacy of lenalidomide combinations with other agents, such as carfilzomib. The phase II multicenter FORTE trial assessed the efficacy and safety of three different carfilzomib-based induction and consolidation approaches in patients with NDMM (n=474).[72] Patients were randomized 1:1:1 to receive four induction cycles with KRd plus ASCT, 12 induction cycles with KRd (KRd12) or carfilzomib, cyclophosphamide and dexamethasone (KCd) plus ASCT. Following consolidation therapy, patients were randomized again to receive lenalidomide with or without carfilzomib. The primary endpoints were 1) the proportion of patients achieving a VGPR or better following induction among patients receiving KRd compared with KCd, and PFS with carfilzomib plus lenalidomide compared with lenalidomide alone following maintenance therapy. FORTE met both primary endpoints. KRd led to a higher rate of VGPR or better versus KCd (70% vs 53%; odds ratio: 2.14 [95% CI: 1.44–3.19]; p=0.0002). Following maintenance, carfilzomib plus lenalidomide proved superior to lenalidomide alone in prolonging PFS (3-year PFS, 75% vs 65%; HR: 0.64 [95% CI: 0.44–0.94]; p=0.023). Similar AE rates leading to discontinuation (approximately 12%) were observed across the groups. The FORTE trial showed that KRd plus ASCT provided better responses compared to the other two treatment approaches.

The phase III ATLAS trial evaluated the efficacy and safety of maintenance therapy with KRd versus lenalidomide in patients with NDMM (n=180).[73] Patients were randomized 1:1 to receive maintenance KRd or lenalidomide alone until disease progression or unacceptable toxicity. After 36 cycles, patients in both arms received lenalidomide maintenance. If patients in the KRd group achieved MRD negativity after cycle 6 and had standard-risk cytogenetics, they were switched to lenalidomide maintenance at cycle 9. The primary endpoint was PFS. In the interim analysis, KRd maintenance led to an improved depth of response compared with the baseline assessment post-ASCT (54% vs 44%; p=0.18) and the MRD negativity rate post-cycle 6 was higher in the KRd arm compared with the lenalidomide alone arm (53% vs 31%; p=0.0035). KRd therapy also improved median PFS versus lenalidomide (59.1 months vs 41.4 months; HR: 0.51 [95% CI: 0.31–0.86]; p=0.012); no significant differences in median OS were observed (not reached vs 61.8 months; HR: 0.83; p=0.68). Similar to FORTE, these data are the first to support KRd maintenance therapy over lenalidomide alone in patients with NDMM who have completed induction therapy plus ASCT.

Nevertheless, the question of the optimal post-ASCT maintenance regimen remains open, particularly whether to use lenalidomide alone or in combination with daratumumab. This challenge frequently arises for patients who undergo transplant off-protocol. Current data from trials such as GRIFFIN and PERSEUS are not definitive on the role of anti-CD38 monoclonal antibodies in maintenance, as neither trial included a second randomization at the time of transplant to explore this question rigorously. While the post-transplant KRd regimen has shown promising efficacy, its use in maintenance is less practical in the real-world setting, especially as carfilzomib is typically not a part of standard induction therapy and, therefore, is less likely to be initiated strictly in the maintenance context. Consequently, the integration of anti-CD38 mAbs in maintenance therapy remains an evolving debate that requires more robust evidence to guide clinical practice. Furthermore, results from ongoing studies evaluating intensification of lenalidomide maintenance are eagerly anticipated. These include MajesTEC-4 and MajesTEC-5 studies evaluating bispecific antibody teclistamab alone[74] or in combination with daratumumab[75]; MagnetisMM-7 trial assessing the maintenance monotherapy using bispecific antibody elranatamab versus single agent lenalidomide; and GEM-BELA-VRd[76] and BLAST[77] trials evaluating the combination of ADC belantamab mafodotin and lenalidomide as post-ASCT maintenance.

Other alternative maintenance strategies include combinations of lenalidomide with iberdomide or selinexor. The multicohort, phase II EMN26 study assessed the effect of three doses of iberdomide (0.75, 1.0 or 1.3 mg) in MM patients who had achieved at least a PR after induction therapy containing a PI plus IMiD followed by single or double ASCT with or without consolidation.[78] The primary endpoint is improvement in response. Results from the first interim analysis of patients who received ≥6 treatment cycles or discontinued earlier were reported at ASH 2023. After 6 treatment cycles of iberdomide, an improvement in response was reported in 35% and 42% of patients treated with 1.0 mg and 1.3 mg, respectively, which was significantly higher than the null hypothesis of ≤20% response improvement within 6 months. The safety profile was manageable, with few non-hematologic AEs. The incidence of grade 3–4 neutropenia was higher among patients receiving 1.3 mg versus 1.0 mg (50% vs 42%). The PFS rates at six months were 91% and 90% in the 1.0 and 1.3 mg cohorts, respectively. Treatment with 1.3 mg led to higher dose reduction and discontinuation rates due to AEs compared with 1.0 mg (45% vs 38% and 10% vs 3%, respectively). These data support further investigation of iberdomide versus lenalidomide maintenance post-ASCT.

At ASH 2023, results from a planned futility analysis of the phase III SeaLAND (ALLG MM23) study were reported which evaluated low-dose selinexor plus lenalidomide in patients with NDMM after at least one prior therapy who had received 3–6 cycles of induction containing bortezomib plus

dexamethasone with or without lenalidomide.[79] Patients were randomized to receive either selinexor plus lenalidomide or lenalidomide alone post-ASCT. The primary endpoint was the 3-year PFS rate. Patients receiving selinexor plus lenalidomide versus lenalidomide alone experienced more grade 3–4 AEs and serious AEs (84% vs 36% and 28% vs 12%). Neutropenia and thrombocytopenia were more common with the combination treatment compared with lenalidomide alone (60.7% vs 28.6% and 24.6% vs 0%). In patients who underwent ASCT, selinexor in combination with lenalidomide as maintenance therapy was generally tolerable. The safety profile was consistent with that previously reported for selinexor and lenalidomide individually.

MRD-directed maintenance therapy in patients with NDMM

Preliminary data from trials presented at ASH 2023 detail several new approaches, including MRD-directed therapies that stratify patients for ASCT or further treatment, and alternative therapies such as the incorporation of iberdomide and selinexor into treatment regimens for newly diagnosed patients. Iberdomide is a novel oral cereblon E3 ligase modulator with improved antitumor and immunostimulatory effects compared with lenalidomide or pomalidomide.[80] Selinexor is an oral selective inhibitor targeting XPO1, a receptor overexpressed in MM,[81] that has been approved for patients after at least one prior therapy.

The phase II RADAR study is a risk-adapted, response-guided trial for transplant-eligible patients with NDMM which aims to determine how to maintain deep responses among MDR-negative patients, deepen responses among MRD-positive patients and optimally manage high-risk patients.[82] The trial design involves induction therapy (lenalidomide, cyclophosphamide, bortezomib and dexamethasone), followed by high-dose melphalan and ASCT. Following ASCT, MRD-negative patients receive 12 cycles of isatuximab maintenance; those who remain MRD-negative are randomized to either continue or stop treatment. MRD-positive patients are included into a multiarmed multistage design to test escalation strategies with different combinations of isatuximab, lenalidomide, bortezomib and dexamethasone. High-risk patients receive Isa-RVd followed by isatuximab with lenalidomide until disease progression.

FREEDMM is a prospective phase II study that uses MRD status to identify patients who can safely stop maintenance therapy following sustained MRD negativity.[83] Eligible patients must have completed at least two years of maintenance therapy post-ASCT and achieved at least a partial response (PR). Those with sustained MRD negativity between Year 1 and Year 2, along with the absence of new bone lesions, are considered for maintenance cessation. MRD-positive patients are excluded from the study. After discontinuation of maintenance therapy, patients will continue to undergo

MRD assessments annually for 3 years. Currently, 31 patients have been enrolled. This ongoing trial will demonstrate the effectiveness of an adaptive MRD-driven strategy in guiding maintenance therapy cessation.

The prospective phase II RAMP UP trial investigates the safety and efficacy of 3-year maintenance therapy with isatuximab plus lenalidomide in patients with MM who are MRD-positive following ASCT.[84] The primary endpoint is the 1-year rate of CR/MRD-negativity. The goal of this trial is to evaluate MRD risk-adapted approaches for maintenance therapy in MM. The phase III MajesTEC-4 trial assessing whether the combination of teclistamab with lenalidomide versus lenalidomide alone as maintenance therapy improves PFS in NDMM patients after ASCT also includes MRD assessment to guide therapy decisions.[74]

Ongoing research in patients with NDMM: Anti-CD38 therapy and beyond

Multiple ongoing trials are assessing the benefits of anti-CD38 mAb-based quadruplet versus triplet therapy in frontline patients (**Table 1**) and doublet/triplet therapy for prolonging the time until disease progression in the maintenance setting (**Table 2**). Several studies are also investigating the impact of intensifying or de-intensifying treatment or deferring ASCT in selected patients based on the MRD response to frontline therapy, in order to further improve patient outcome as reflected both by clinical benefit and improved quality of life, so more meaningfully translating to real world practice.[85]

Recently, a BCMA-targeting ADC belantamab mafodotin (belamaf) has been evaluated as frontline treatment in MM. Belamaf has conferred a significant PFS benefit in combination with bortezomib and dexamethasone[86] or pomalidomide and dexamethasone[87] in patients with R/R MM, providing a rationale for investigating belamaf-containing regimens in NDMM. The ongoing the phase I/II BelaRd trial investigates belamaf plus Rd in transplant-ineligible patients with NDMM.[88] Part 1 of this study aimed to evaluate the safety and tolerability of three belamaf doses (2.5, 1.9 and 1.4 mg/kg) in 36 patients and establish the recommended phase II dose (RP2D). At a median follow-up of 20.3 months, the most common non-ocular grade ≥3 TEAEs were fatigue (58%), diarrhea (22%), rash (17%), COVID-19 (14%), and insomnia (11%). Regarding ocular AEs, a meaningful decline in best corrected visual acuity with at least a three-line drop in the better-seeing eye, was observed in 10%, 10% and 8% of patients treated with 2.5, 1.9 and 1.4 mg/kg belamaf, respectively. The most frequently reported grade ≥3 ocular AE was decreased vision (4%); grade ≥3 keratopathy was reported in <2% of the assessments. The ORR was 100% across all patient groups, with CR or better achieved in 58%, 50% and 50% of patients treated with 2.5, 1.9 and

1.4 mg/kg, respectively. No disease progression was observed, the median PFS and median time to progression were not reached, and responses continued to deepen across all treatment doses.

In a recently published analysis of the phase II GEM-BELA-VRD trial, the combination of belamaf and RVd demonstrated efficacy and manageable toxicity in transplant-eligible patients with NDMM.[89] The ORR was 94% during all treatment phases, with CR rates of 36%, 56%, 70%, and 82% during induction, ASCT, consolidation and one year of maintenance, respectively. The MRD negativity rates were 60.9%, 69.0%, 84.2% and 91.2% during each treatment phase, respectively.

In the ongoing phase I DREAMM-9 study, belamaf plus RVd/Rd showed early and deep anti-myeloma responses in transplant-ineligible NDMM patients.[90] RVd was administered every three weeks (Q3W) until cycle 8, followed by Rd every four weeks (Q4W). The study included seven cohorts which received different belamaf treatment regimens: 1.9 mg/kg Q3/4W (Cohort 1), 1.4 mg/kg Q6/8W (Cohort 2), 1.9 mg/kg Q6/8W (Cohort 3), 1.0 mg/kg Q3/4W (Cohort 4), 1.4 mg/kg Q3/4W (Cohort 5), 1.4 mg/kg 9W to 1.0 mg/kg Q9/12W (Cohort 6) and 1.9 mg/kg (9W) to 1.4 mg/kg Q9/12W (Cohort 7). In an interim analysis, VGPR or better was observed in 79% of patients in Cohorts 1–6 and CR or better was observed in up to 83.3% of patients in Cohorts 2 and 3. High rates of MRD negativity were observed in patients who achieved VGPR or better. No new safety signals were reported, and the incidence of corneal AEs decreased with dose reductions and longer intervals between doses.

Conclusions

- Clinical research on NDMM is a rapidly evolving field with great advances in recent years, leading to the expansion of the clinical armamentarium and improvements in outcome, especially in terms of reducing toxicity while preserving efficacy.
- Recent clinical research has demonstrated the benefit of quadruplet therapy with anti-CD38 mAbs over triplet therapy, thus establishing quadruplet regimens as a new standard of care in NDMM, as well as the evolving role of maintenance.
- Active research is ongoing to meet the urgent need to treat patients who are ineligible for ASCT, as well as to define the optimal post-transplant maintenance strategy.

Table 1. Ongoing frontline trials in patients with newly diagnosed multiple myeloma.

Study	Phase	Frontline regimens	Setting	Primary endpoint	Initial completion
PERSEUS / EMN17 (NCT03710603)[91]	III	D-RVd vs RVd	Transplant-eligible patients	PFS	May 2025
ADVANCE (NCT04268498)[92]	II	D-KRd vs KRd	Transplant-eligible patients, MRD-adapted therapy (no ASCT if MRD-neg after 8 cycles)	MRD-neg rate	February 2027
EMN18 (NCT03896737)[93]	II	D-VCd vs VTd, followed by Dara plus ixazomib vs ixazomib maintenance	Transplant-eligible patients	• PFS • MRD-neg rate	May 2024
GEM21menos65 (NCT05558319)[94]	III	Isa-Vd + iberdomide vs Isa-RVd vs RVd	Transplant-eligible patients	MRD-neg rate	April 2027
CEPHEUS (NCT03652064)[95]	III	D-RVd vs RVd	Transplant-eligible patients without intent for upfront ASCT+ transplant-ineligible patients	MRD-neg rate	August 2025
EQUATE (NCT04566328)[96]	III	D-RVd vs D-Rd	Transplant-eligible patients without intent for upfront ASCT and transplant-ineligible patients	OS	December 2027
IMROZ (NCT03319667)[97]	III	Isa-RVd vs RVd	Transplant-ineligible patients	PFS	April 2026
BENEFIT (NCT04751877)[98]	III	Isa-RVd vs Isa-Rd	Transplant-ineligible fit patients, aged 65–80 years	MRD rate at 18 months	April 2024
BelaRd (NCT04808037)[88]	I/II	Belamaf + Rd	Transplant-ineligible patients	RP2D (Part 1), safety/ efficacy at RP2D (Part 2)	September 2028
GEM-BELA-VRD (NCT04802356)[89]	II	Belamaf + RVd	Transplant-eligible patients	Safety	March 2025
DREAMM-9 (NCT04091126)[90]	I	Belamaf + RVd/Rd	Transplant-ineligible patients	Safety	November 2024

ASCT, autologous stem cell transplantation; Belamaf, belantamab mafodotin; D, Dara, daratumumab; Isa, isatuximab; MRD-neg, minimal residual disease negativity; OS, overall survival; PFS, progression-free survival; RP2D, recommended phase II dose; RVd, lenalidomide, bortezomib and dexamethasone; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone; VCd, bortezomib, cyclophosphamide and dexamethasone; VTd, bortezomib, thalidomide and dexamethasone.

- Many trials are currently testing MRD-driven approaches to better select patients who are likely to benefit from specific therapeutic approaches, with the option of deferring ASCT in selected patients becoming an increasingly important consideration in the transplant eligible population.

Conflict of interest

Clifton Mo acted on the advisory boards for AbbVie, BMS, GSK, Janssen, Karyopharm, Sanofi and Takeda, and as a consultant for AbbVie, Janssen, Karyopharm and Sanofi. Monique Hartley-Brown received honoraria for

Table 2. Ongoing maintenance trials for patients with newly diagnosed multiple myeloma (NDMM).

Ongoing studies	Phase	Maintenance regimens	Setting	Primary endpoint	Initial completion
Anti-CD38 mAb-based doublet/triplet therapies					
AURIGA (NCT03901963)[99]	III	Dara plus lenalidomide vs lenalidomide alone	Post-ASCT	MRD-neg rate	June 2024
DRAMMATIC (NCT04071457)[100]	III	Dara plus lenalidomide vs lenalidomide alone	Post-ASCT	OS	July 2029
NCT05776979[101]	II	Isa plus lenalidomide	Post-ASCT in high-risk NDMM	3-year PFS	December 2025
HEME-18 (NCT05344833)[102]	II	Isa plus lenalidomide	MRD-pos patients post-ASCT	MRD-neg CR rate	December 2030
GMMG-CONCEPT (NCT03104842)[103]	II	Isa-KRd	Post-ASCT in high-risk NDMM	MRD-neg rate	February 2025
GEM-OPTIMAL (NCT05218603)[103]	N/A	Dara plus bortezomib	Post-D-VMP in non-transplant patients	PFS	November 2025
Novel combinations and therapies					
UK-MRA Myeloma XIV FiTNEss trial (NCT03720041)[104]	III	Ixazomib plus lenalidomide vs lenalidomide alone	Transplant-ineligible patients, post-ixazomib-Rd induction therapy	PFS	December 2024
EXCALIBER-Maintenance (NCT05827016)[105]	III	Iberdomide vs lenalidomide alone	Post-ASCT	PFS	March 2029
IBEX (NCT06107738)[106]	II	Iberdomide plus Dara	Post-ASCT	MRD-neg rate at 12 months	December 2025
KarMMa-9 (NCT06045806)[107]	III	Ide-cel plus lenalidomide vs lenalidomide alone	Suboptimal response, post-ASCT	PFS	March 2031
CARTITUDE-5 (NCT04923893)[108]	III	Cilta-cel vs Rd	Post-RVd induction, non-transplant setting	PFS	June 2026
MajesTEC-4 (NCT05243797)[74]	III	Teclistamab plus lenalidomide vs teclistamab vs lenalidomide alone	Post-ASCT	PFS	April 2028
MajesTEC-5 (NCT05695508)[75]	II	Teclistamab plus Dara plus lenalidomide	Post-ASCT	Safety	May 2026
ISA-HC-NK (NCT04558931)[85]	II	CellProtect NK cells plus Isa vs Isa alone	Post-ASCT	• VGPR rate • MRD-neg rate	December 2027

ASCT, autologous stem cell transplantation; Cilta-cel, ciltacabtagene autoleucel; CR, complete response; Dara, daratumumab; Ide-cel, idecabtagene vicleucel; Isa, isatuximab; KRd, carfilzomib, lenalidomide and dexamethasone; mAb, monoclonal antibody; MRD-neg, minimal residual disease negativity; N/A, not applicable; OS, overall survival; PFS, progression-free survival; RVd, lenalidomide, bortezomib and dexamethasone; Rd, lenalidomide and dexamethasone; VGPR, very good partial response; VMP, bortezomib, melphalan and prednisone.

consultancy from AbbVie, Bristol Myers Squibb/Celgene, GSK, Janssen, Karyopharm and Sanofi, and speaker's honoraria from Multiple Myeloma Research Foundation and Cancer Care. Shonali Midha reported Abbvie stock ownership and honoraria for consultancy from Janssen and Pfizer. Adam S. Sperling has acted as a consultant for Novartis and Roche. Giada

Bianchi received honoraria for consultancy from Prothena. Omar Nadeem reports honorarium from Pfizer; advisory board participation for BMS, Janssen, Takeda, Sanofi, GPCR Therapeutics; and research funding from Takeda, Janssen. Betsy O'Donnell has received honoraria for advisory board meetings from Janssen, BMS, Sanofi, Pfizer, ExactSciences and Grail; honoraria for consultancy from Takeda; as well as steering committee involvement with Natera and Legend Pharmaceuticals. Paul Richardson received honoraria for consultancy from Celgene/BMS, GSK, Karyopharm, Oncopeptides, Regeneron and Sanofi as well as research grants from Oncopeptides. Yuxin Liu and Jacob Laubach have no conflicts to disclose. These funding entities did not play a role in the development of the manuscript and did not influence its content in any way.

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REFERENCES

1. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(3):309-322. doi:10.1016/j.annonc.2020.11.014

2. Cancer Stat Facts: Myeloma. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. Accessed October 2024. https://seer.cancer.gov/statfacts/html/mulmy.html

3. Andres M, Feller A, Rohrmann S, et al. Survival improvements in Multiple Myeloma Patients in Switzerland. 2019:39.

4. Noll JE, Williams SA, Tong CM, et al. Myeloma plasma cells alter the bone marrow microenvironment by stimulating the proliferation of mesenchymal stromal cells. *Haematologica*. 2014;99(1):163-171. doi:10.3324/haematol.2013.090977

5. Willrich MAV, Katzmann JA. Laboratory testing requirements for diagnosis and follow-up of multiple myeloma and related plasma cell dyscrasias. *Clin Chem Lab Med*. 2016;54(6):907-919. doi:10.1515/cclm-2015-0580

6. Bladé J, Rosiñol L, Cibeira MT, Rovira M, Carreras E. Hematopoietic stem cell transplantation for multiple myeloma beyond 2010. *Blood*. 2010;115(18):3655-3663. doi:10.1182/blood-2009-08-238196

7. Schmidt A. The Gaining Momentum of BCMA-Directed Therapies for Relapsed/Refractory Multiple Myeloma. *healthbook TIMES Onco Hema*. 2023;17(3):56-62. doi:10.36000/hbT.OH.2023.17.123

8. Schmidt A. Multiple Myeloma with a Special Focus on Precision Medicine. *healthbook TIMES Onco Hema*. 2020;6(4):36-46. doi:10.36000/hbT.OH.2020.06.023

9. Cowan AJ, Green DJ, Kwok M, et al. Diagnosis and Management of Multiple Myeloma: A Review. *JAMA*. 2022;327(5):464-477. doi:10.1001/jama.2022.0003

10. Usmani SZ, Hoering A, Cavo M, et al. Clinical predictors of long-term survival in newly diagnosed transplant eligible multiple myeloma - an IMWG Research Project. *Blood Cancer J*. 2018;8(12):123. doi:10.1038/s41408-018-0155-7

11. Mohty M, Terpos E, Mateos MV, et al. Multiple Myeloma Treatment in Real-world Clinical Practice: Results of a Prospective, Multinational, Noninterventional Study. *Clin Lymphoma Myeloma Leuk*. 2018;18(10):e401-e419. doi:10.1016/j.clml.2018.06.018

12. Eisfeld C, Kajüter H, Möller L, Wellmann I, Shumilov E, Stang A. Time trends in survival and causes of death in multiple myeloma: a population-based study from Germany. *BMC Cancer*. 2023;23(1):317. doi:10.1186/s12885-023-10787-5

13. Deaglio S, Mehta K, Malavasi F. Human CD38: a (r)evolutionary story of enzymes and receptors. *Leuk Res*. 2001;25(1):1-12. doi:10.1016/s0145-2126(00)00093-x

14. Bisht K, Fukao T, Chiron M, et al. Immunomodulatory properties of CD38 antibodies and their effect on anticancer efficacy in multiple myeloma. *Cancer Med*. 2023;12(20):20332-20352. doi:10.1002/cam4.6619

15. van de Donk NWCJ, Usmani SZ. CD38 Antibodies in Multiple Myeloma: Mechanisms of Action and Modes of Resistance. *Front Immunol*. 2018;9:2134. doi:10.3389/fimmu.2018.02134

16. Leleu X, Martin T, Weisel K, et al. Anti-CD38 antibody therapy for patients with relapsed/refractory multiple myeloma: differential mechanisms of action and recent clinical trial outcomes. *Ann Hematol*. 2022;101(10):2123-2137. doi:10.1007/s00277-022-04917-5

17. Malavasi F, Faini AC. Mechanism of Action of a New Anti-CD38 Antibody: Enhancing Myeloma Immunotherapy. *Clin Cancer Res*. 2019;25(10):2946-2948. doi:10.1158/1078-0432.Ccr-19-0260

18. Deckert J, Wetzel MC, Bartle LM, et al. SAR650984, A Novel Humanized CD38-Targeting Antibody, Demonstrates Potent Antitumor Activity in Models of Multiple Myeloma and Other CD38+ Hematologic Malignancies. *Clin Cancer Res*. 2014;20(17):4574-4583. doi:10.1158/1078-0432.Ccr-14-0695

19. Zhu C, Song Z, Wang A, et al. Isatuximab Acts Through Fc-Dependent, Independent, and Direct Pathways to Kill Multiple Myeloma Cells. *Front Immunol*. 2020;11:1771. doi:10.3389/fimmu.2020.01771

20. Hashmi H, Husnain M, Khan A, Usmani SZ. CD38-Directed Therapies for Management of Multiple Myeloma. *Immunotargets Ther*. 2021;10:201-211. doi:10.2147/itt.S259122

21. Costello CL. Newly diagnosed multiple myeloma: making sense of the menu. *Hematology Am Soc Hematol Educ Program*. 2022;2022(1):539-550. doi:10.1182/hematology.2022000404

22. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Multiple Myeloma Version 3. NCCN. Accessed April 2024. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf

23. Hanamura I. Gain/Amplification of Chromosome Arm 1q21 in Multiple Myeloma. *Cancers (Basel)*. 2021;13(2):256. doi:10.3390/cancers13020256

24. Kadam Amare P, Nikalje Khasnis S, Hande P, et al. Cytogenetic Abnormalities in Multiple Myeloma: Incidence, Prognostic Significance, and Geographic Heterogeneity in Indian and Western Populations. *Cytogenet Genome Res*. 2023;162(10):529-540. doi:10.1159/000529191

25. Caro J, Al Hadidi S, Usmani S, Yee AJ, Raje N, Davies FE. How to Treat High-Risk Myeloma at Diagnosis and Relapse. *Am Soc Clin Oncol Educ Book*. 2021;41:291-309. doi:10.1200/EDBK_320105

26. Hanamura I. Multiple myeloma with high-risk cytogenetics and its treatment approach. *Int J Hematol*. 2022;115(6):762-777. doi:10.1007/s12185-022-03353-5

27. Wang J, Li J, Zhang R, Li J, Chen L, Jin Y. Real-world prognostic significance of attaining minimal residual disease negativity in newly diagnosed multiple myeloma. *Discov Oncol*. 2024;15(1):38. doi:10.1007/s12672-024-00891-8

28. Kumar SK, Callander NS, Adekola K, et al. Multiple Myeloma, Version 3.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2020;18(12):1685-1717. doi:10.6004/jnccn.2020.0057

29. Richardson PG, Durie BG, Rosiñol L, et al. Clinical perspectives on the optimal use of lenalidomide plus bortezomib and dexamethasone for the treatment of newly diagnosed multiple myeloma. *Haematologica*. 2023;108(11):2894-2912. doi:10.3324/haematol.2022.282624

30. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. *Lancet*. 2019;394(10192):29-38. doi:10.1016/s0140-6736(19)31240-1

31. Glaría E, Valledor AF. Roles of CD38 in the Immune Response to Infection. *Cells*. 2020;9(1):228. doi:10.3390/cells9010228

32. Facon T, Kumar SK, Weisel K, et al. Daratumumab Plus Lenalidomide and Dexamethasone in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma: Maia Age Subgroup Analysis. *Blood*. 2022;140(suppl_1):10133-10136. doi:10.1182/blood-2022-163555

33. Goldschmidt H, Mai EK, Bertsch U, et al. Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. *Lancet Haematol*. 2022;9(11):e810-e821. doi:10.1016/S2352-3026(22)00263-0

34. Older Fit Patients with NDMM May Benefit from Alternative Induction Therapy. Hematology ADVISOR. Accessed April 2024. https://www.hematologyadvisor.com/reports/older-fit-patients-ndmm-may-benefit-alternative-induction-therapy/

35. Facon T, Kumar S, Plesner T, et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. *N Engl J Med*. 2019;380(22):2104-2115. doi:10.1056/NEJMoa1817249

36. Weisel K, Kumar S, Moreau P, et al. P09 Daratumumab plus Lenalidomide and dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma (ndmm): Updated Analysis of the Phase 3 MAIA Study. Presented at: EHA 2023; 09–11 June 2023. Frankfurt, Germany. Oral presentation P09. doi:10.1097/01.HS9.0000936164.84357.ed

37. Facon T, Cook G, Usmani SZ, et al. Daratumumab plus lenalidomide and dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: frailty subgroup analysis of MAIA. *Leukemia*. 2022;36(4):1066-1077. doi:10.1038/s41375-021-01488-8

38. Moreau P, Facon T, Usmani S, et al. Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Transplant-Ineligible Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM): Clinical Assessment of Key Subgroups of the Phase 3 Maia Study. *Blood*. 2022;140(suppl_1):7297-7300. doi:10.1182/blood-2022-163494

39. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2024;390(4):301-313. doi:10.1056/NEJMoa2312054

40. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Phase 3 Randomized Study of Daratumumab (DARA) + Bortezomib, Lenalidomide, and Dexamethasone (VRd) Versus Vrd Alone in Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM) Who Are Eligible for Autologous Stem Cell Transplantation (ASCT): Primary Results of the Perseus Trial. Presented at: ASH 2023; 07–10 December 2023. San Diego, California, USA. Paper presentation session LBA-1.

41. Sonneveld P, Moreau P, Dimopoulos MA, et al. Daratumumab + bortezomib/lenalidomide/dexamethasone in transplant-eligible patients with newly diagnosed multiple myeloma (NDMM): Analysis of minimal residual disease in the PERSEUS trial. Presented at: EHA2024 Hybrid Congress; 13–16 June 2024. Madrid, Spain. Oral presentation S201.

42. Voorhees PM, Sborov DW, Laubach J, et al. Addition of daratumumab to lenalidomide, bortezomib, and dexamethasone for transplantation-eligible patients with newly diagnosed multiple myeloma (GRIFFIN): final analysis of an open-label, randomised, phase 2 trial. *Lancet Haematol*. 2023;10(10):e825-e837. doi:10.1016/s2352-3026(23)00217-x

43. Costa LJ, Chhabra S, Medvedova E, et al. Minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma (MASTER): final report of the multicentre, single-arm, phase 2 trial. *Lancet Haematol*. 2023;10(11):e890-e901. doi:10.1016/s2352-3026(23)00236-3

44. Giri S, Chhabra S, Medvedova E, et al. Quadruplet Induction, Autologous Transplantation and Minimal Residual Disease Adapted Consolidation and Treatment Cessation in Older Adults ≥70y with Newly Diagnosed Multiple Myeloma: A Subgroup Analysis of the Master Trial. Presented at: ASH 2022; 10–13 December 2022. New Orleans, Louisiana, USA. Poster session 1930.

45. Touzeau C, Perrot A, Hulin C, et al. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone Induction and Consolidation with Tandem Transplant in High-Risk Newly Diagnosed Myeloma Patients: Final Results of the Phase 2 Study IFM 2018-04. Presented at: ASH 2023; 07–10 December 2023. San Diego, California, USA. Presentation session 207.

46. Landgren O, Hultcrantz M, Diamond B, et al. Safety and Effectiveness of Weekly Carfilzomib, Lenalidomide, Dexamethasone, and Daratumumab Combination Therapy for Patients With Newly Diagnosed Multiple Myeloma: The MANHATTAN Nonrandomized Clinical Trial. *JAMA Oncol*. 2021;7(6):862-868. doi:10.1001/jamaoncol.2021.0611

47. Mateos MV, Paiva B, Cedena Romero MT, et al. GEM2017FIT Trial: Induction Therapy with Bortezomib-Melphalan and Prednisone (VMP) Followed By Lenalidomide and Dexamethasone (Rd) Versus Carfilzomib, Lenalidomide and Dexamethasone (KRd) Plus/Minus Daratumumab (D), 18 Cycles, Followed By Consolidation and Maintenance Therapy with Lenalidomide and Daratumumab: Phase III, Multicenter, Randomized Trial for Elderly Fit Newly Diagnosed Multiple Myeloma (NDMM) Patients Aged between 65 and 80 Years. Presented at: ASH 2023; 07–10 December 2023. San Diego, California, USA. Presentation session 209.

48. Usmani S et al. Daratumumab SC + Bortezomib/Lenalidomide/Dexamethasone in Patients With Transplant-ineligible or Transplant-deferred Newly Diagnosed Multiple Myeloma: Results of the Phase 3 CEPHEUS Study. Presented at: 21st International Myeloma Society Annual Meeting & Exposition; 25–28 September 2024. Rio De Janeiro, Brazil. Oral presentation OA-63. doi:10.1016/S2152-2650(24)02344-9

49. Gay F, Roeloffzen W, Dimopoulos MA, et al. Results of the Phase III Randomized Iskia Trial: Isatuximab-Carfilzomib-Lenalidomide-Dexamethasone Vs Carfilzomib-Lenalidomide-Dexamethasone As Pre-Transplant Induction and Post-Transplant Consolidation in Newly Diagnosed Multiple Myeloma Patients. Presented at: ASH 2023; 07–10 December 2023. San Diego, California, USA. Presentation session 4.

50. The IsKia Trial: Diving Into Deeper Responses for Multiple Myeloma. ASH Publications. Accessed April 2024. https://ashpublications.org/ashnewsdaily/news/7641/The-IsKia-Trial-Diving-Into-Deeper-Responses-for

51. Raab MS, Mai EK, Bertsch U, et al. Isatuximab, lenalidomide, bortezomib and dexamethasone for newly-diagnosed, transplant-eligible multiple myeloma: Post transplantation interim analysis of the randomized phase III GMMG-HD7 trial. Presented at: EHA2024 Hybrid Congress; 13–16 June 2024. Madrid, Spain. Oral presentation S202.

52. O'Donnell EK, Mo CC, Yee AJ, et al. A Phase II Study of Isatuximab, Once Weekly Carfilzomib, Lenalidomide, Dexamethasone, in Newly Diagnosed, Transplant-Eligible Multiple Myeloma (The SKylaRk Trial). Presented at: ASH 2023; 07–10 December 2023. San Diego, California, USA. Presentation session 3239.

53. O'Donnell E, Mo C, Yee AJ, et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone in patients with newly diagnosed, transplantation-eligible multiple myeloma (SKylaRk): a single-arm, phase 2 trial. *Lancet Haematol*. 2024;11(6):e415-e424. doi:10.1016/S2352-3026(24)00070-X

54. Leypoldt LB, Tichy D, Besemer B, et al. Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone for the Treatment of High-Risk Newly Diagnosed Multiple Myeloma. *J Clin Oncol*. 2023;42(1):26-37. doi:10.1200/jco.23.01696

55. Facon T, Dimopoulos MA, Leleu XP, et al. Phase 3 study results of isatuximab, bortezomib, lenalidomide, and dexamethasone (Isa-VRd) versus VRd for transplant-ineligible patients with newly diagnosed multiple myeloma (IMROZ). *J Clin Oncol*. 2024;42(suppl_16):7500. doi:10.1200/JCO.2024.42.16_suppl.7500

56. Facon T, Dimopoulos MA, Leleu X, et al. Phase 3 study results of isatuximab, bortezomib, lenalidomide, and dexamethasone (Isa-VRD) versus VRD for transplant-ineligible patients with newly diagnosed multiple myeloma (IMROZ). Presented at: EHA2024 Hybrid Congress; 13–16 June 2024. Madrid, Spain. Oral presentation S100. doi:10.1200/JCO.2024.42.16_suppl.7500

57. Leleu XP, Hulin C, Lambert J, et al. Phase 3 randomized study of isatuximab (Isa) plus lenalidomide and dexamethasone (Rd) with bortezomib versus isard in patients with newly diagnosed transplant ineligible multiple myeloma (NDMM TI). *J Clin Oncol*. 2024;42(suppl_16):7501. doi:10.1200/JCO.2024.42.16_suppl.7501

58. Leleu XP, Hulin C, Lambert J, et al. Phase 3 randomized study of isatuximab (Isa) plus lenalidomide and dexamethasone (Rd) with bortezomib versus isard in patients with newly diagnosed transplant ineligible multiple myeloma (NDMM TI). Presented at: EHA2024 Hybrid Congress; 13–16 June 2024. Madrid, Spain. Oral presentation S203. doi:10.1200/JCO.2024.42.16_suppl.7501

59. Leleu X, Hulin C, Lambert J, et al. Isatuximab, lenalidomide, dexamethasone and bortezomib in transplant-ineligible multiple myeloma: the randomized phase 3 BENEFIT trial. *Nat Med*. 2024;30:2235-2241. doi:10.1038/s41591-024-03050-2

60. Ocio EM, Perrot A, Bories P, et al. Efficacy and safety of isatuximab plus bortezomib, lenalidomide, and dexamethasone in patients with newly diagnosed multiple myeloma ineligible/with no immediate intent for autologous stem cell transplantation. *Leukemia*. 2023;37(7):1521-1529. doi:10.1038/s41375-023-01936-7

61. Ocio EM, Bringhen S, Martinez-Lopez J, et al. Phase 1b Study of Isatuximab in Combination With Bortezomib, Cyclophosphamide, and Dexamethasone in Newly Diagnosed, Transplant-ineligible Multiple Myeloma Patients. *Hemasphere*. 2023;7(2):e829. doi:10.1097/hs9.0000000000000829

62. Minimal Residual Disease Adapted Strategy (MIDAS). Veeva. Accessed April 2024. https://ctv.veeva.com/study/minimal-residual-disease-adapted-strategy

63. Landgren O, Maura F, Kazandjian D. Advance Multicenter Clinical Trial: MRD-Driven Therapy in Newly Diagnosed Multiple Myeloma Patients. *Blood*. 2023;142(suppl_1):3392. doi:10.1182/blood-2023-186834

64. Mo CC, Hartley-Brown MA, Midha S, et al. Upfront or Deferred Autologous Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma in the Era of Triplet and Quadruplet Induction and Minimal Residual Disease/Risk-Adapted Therapy. *Cancers (Basel)*. 2023;15(24):5709. doi:10.3390/cancers15245709

65. Richardson PG. The Role of Autologous Stem Cell Transplantation in the Treatment of Newly Diagnosed Multiple Myeloma: Is It Time to Rethink the Paradigm in the Era of Targeted Therapy? *Hemato*. 2024;5(2):144-156. doi:10.3390/hemato5020012

66. Coffey DG, Maura F, Gonzalez-Kozlova E, et al. Immunophenotypic correlates of sustained MRD negativity in patients with multiple myeloma. *Nat Commun*. 2023;14(1):5335. doi:10.1038/s41467-023-40966-8

67. 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. doi:10.1056/NEJMoa2204925

68. Richardson PG, Zonder JA, Khan AM, et al. Outcomes in African-American (AA) and white patients with newly diagnosed multiple myeloma receiving RVd-alone vs RVd+ASCT in DETERMINATION: efficacy, safety, and second primary malignancies (SPMS). Presented at: EBMT 2024 Annual Meeting; 14-17 April 2024. Glasgow, United Kingdom. Oral presentation OS10-05.

69. Zonder JA, Khan A, Jacobus SJ, et al. Treatment Outcomes and Prognostic Factors with Lenalidomide, Bortezomib, and Dexamethasone (RVd) Alone Versus Rvd Plus Autologous Stem Cell Transplantation (ASCT) in African American (AA) Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM) in the Determination Phase 3 Trial. Presented at: ASH 2023; 07–10 December 2023. San Diego, California, USA. Presentation session 4762.

70. Richardson PG, Jacobus SJ, Weller E, et al. Lenalidomide, bortezomib, and dexamethasone (RVd) ± autologous stem cell transplantation (ASCT) and R maintenance to progression for newly diagnosed multiple myeloma (NDMM): The phase 3 DETERMINATION trial. Presented at: 2022 ASCO Annual Meeting; 03–07 June 2022. Chicago, USA. Presentation LBA4.

71. Gupta RK, Gupta A, Hillengass J, et al. A review of the current status of lenalidomide maintenance therapy in multiple myeloma in 2022. *Expert Rev Anticancer Ther*. 2022;22(5):457-469. doi:10.1080/14737140.2022.2069564

72. Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. *Lancet Oncol*. 2021;22(12):1705-1720. doi:10.1016/s1470-2045(21)00535-0

73. Dytfeld D, Wróbel T, Jamroziak K, et al. Carfilzomib, lenalidomide, and dexamethasone or lenalidomide alone as maintenance therapy after autologous stem-cell transplantation in patients with multiple myeloma (ATLAS): interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2023;24(2):139-150. doi:10.1016/s1470-2045(22)00738-0

74. Phase 3 Study of Teclistamab in Combination With Lenalidomide and Teclistamab Alone Versus Lenalidomide Alone in Participants With Newly Diagnosed Multiple Myeloma as Maintenance Therapy Following Autologous Stem Cell Transplantation (MajesTEC-4). ClinicalTrials.gov. Accessed April 2024. https://www.clinicaltrials.gov/study/NCT05243797

75. GMMG-HD10 / DSMM-XX / 64007957MMY2003, MajesTEC-5 (HD10/DSMMXX). ClinicalTrials.gov. Accessed April 2024. https://www.clinicaltrials.gov/study/NCT05695508

76. Gonzalez-Calle V, Rodriguez Otero P, Rey-Bua B, et al. Belantamab Mafodotin in Combination with Vrd for the Treatment of Newly Diagnosed Transplant Eligible Multiple Myeloma Patients: Results from the Phase II, Open Label, Multicenter, GEM-BELA-Vrd Trial. *Blood*. 2022;140(suppl_1):7286-7288. doi:10.1182/blood-2022-162584

77. Cohen AD, Garfall AL, Susanibar S, et al. Phase 2 Study of Belantamab Mafodotin As Pre- and Post-Stem Cell Transplant Consolidation and Maintenance (BLAST study) for Multiple Myeloma Patients in First Remission. *Blood*. 2022;140(suppl_1):12628-12629. doi:10.1182/blood-2022-165526

78. van de Donk NWCJ, Touzeau C, Terpos E, et al. 208 Iberdomide Maintenance after Autologous Stem-Cell Transplantation in Newly Diagnosed MM: First Results of the Phase 2 EMN26 Study. Presented at: ASH 2023; 07–10 December 2023. San Diego, California, USA. Oral presentation session 208. doi:10.1182/blood-2023-177564

79. Quach H, Lasica M, Low M, et al. Planned Interim Safety Analysis of the Phase 3 Randomized Trial of Selinexor and Lenalidomide Versus Lenalidomide Maintenance Post Autologous Stem Cell Transplant for Patients with Newly Diagnosed Multiple Myeloma (ALLG MM23; Sealand). Presented at: ASH 2023; 07–10 December 2023. San Diego, California, USA. Poster 2023. doi:10.1182/blood-2023-185169

80. Bjorklund CC, Kang J, Amatangelo M, et al. Iberdomide (CC-220) is a potent cereblon E3 ligase modulator with antitumor and immunostimulatory activities in lenalidomide- and pomalidomide-resistant multiple myeloma cells with dysregulated CRBN. *Leukemia*. 2020;34(4):1197-1201. doi:10.1038/s41375-019-0620-8

81. Mo CC, Yee AJ, Midha S, et al. Selinexor: Targeting a novel pathway in multiple myeloma. *EJHaem*. 2023;4(3):792-810. doi:10.1002/jha2.709

82. Ramasamy K, Cairns DA, Royle KL, et al. RADAR Trial: MRD Response Adapted Trial for Newly Diagnosed Transplant Eligible Myeloma Patients. Presented at: ASH 2023; 07–10 December 2023. San Diego, California, USA. Poster 3390.

83. Avila Rodriguez AM, Hadidi D, Hofmeister CC, et al. Free from Drug Therapy in Multiple Myeloma (FREEDMM): MRD-Based Cessation of Maintenance. Presented at: ASH 2023; 07–10 December 2023. San Diego, California, USA. Poster 3395. doi:10.1182/blood-2023-190011

84. Sweiss K, Hofmeister CC, Mohyuddin GR, et al. RAMP up: Risk Adapted Post-Autologous Transplant Maintenance Therapy in MRD Positive Myeloma Patients. Presented at: ASH 2023; 07–10 December 2023. San Diego, California, USA. Poster 4974.

85. 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. doi:10.1038/s41408-018-0141-0

86. Hungria V, Robak P, Hus M, et al. Belantamab Mafodotin, Bortezomib, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2024;391(5):393-407. doi:10.1056/NEJMoa2405090

87. Dimopoulos MA, Beksac M, Pour L, et al. Belantamab Mafodotin, Pomalidomide, and Dexamethasone in Multiple Myeloma. *N Engl J Med*. 2024;391(5):408-421. doi:10.1056/NEJMoa2403407

88. Terpos E, Gavriatopoulou M, Ntanasis-Stathopoulos I, et al. Long-Term Safety and Efficacy Results of Belantamab Mafodotin Plus Lenalidomide and Dexamethasone in Transplant Ineligible Patients with Newly Diagnosed Multiple Myeloma: An Updated Part 1 Analysis from the Phase 1/2 Belard Trial. *Blood*. 2023;142(suppl_1):4765. doi:10.1182/blood-2023-173064

89. González-Calle V, Rey-Bua B, Puertas B, et al. Belantamab mafodotin in combination with VRd for the treatment of newly diagnosed transplant eligible multiple myeloma patients: results from the phase II, open label, multicenter, GEM-BELA-VRd trial. Presented at: 21st International Myeloma Society Annual Meeting & Exposition; 25–28 September 2024. Rio De Janeiro, Brazil. Oral presentation OA-64. doi:10.1016/S2152-2650(24)02345-0

90. Usmani SZ, Mielnik M, Byun JM, et al. A phase 1 study of belantamab mafodotin in combination with standard of care in newly diagnosed multiple myeloma: An interim analysis of DREAMM-9. *J Clin Oncol*. 2023;41(suppl_16):8018. doi:10.1200/JCO.2023.41.16_suppl.8018

91. Daratumumab, VELCADE (Bortezomib), Lenalidomide and Dexamethasone Compared to VELCADE, Lenalidomide and Dexamethasone in Subjects With Previously Untreated Multiple Myeloma (Perseus). ClinicalTrials.gov. Accessed April 2024. https://www.clinicaltrials.gov/study/NCT03710603

92. A Study of Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Newly-Diagnosed Multiple Myeloma (ADVANCE). ClinicalTrials.gov. Accessed April 2024. https://clinicaltrials.gov/study/NCT04268498

93. Daratumumab-bortezomib-dexamethasone (Dara-VCd) vs Bortezomib-Thalidomide-Dexamethasone (VTd), Then Maintenance With Ixazomib (IXA) or IXA-Dara. ClinicalTrials.gov. Accessed April 2024. https://clinicaltrials.gov/study/NCT03896737

94. NDMM Patients Candidates for ASCT Comparing Extended VRD Plus vs. Isa-VRD vs. Isa-V-Iberdomide (GEM21menos65). ClinicalTrials.gov. Accessed April 2024. https://clinicaltrials.gov/study/NCT05558319

95. A Study Comparing Daratumumab, VELCADE (Bortezomib), Lenalidomide, and Dexamethasone (D-VRd) With VELCADE, Lenalidomide, and Dexamethasone (VRd) in Participants With Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy. ClinicalTrials.gov. Accessed April 2024. https://clinicaltrials.gov/study/NCT03652064

96. Testing the Use of Combination Therapy in Adult Patients With Newly Diagnosed Multiple Myeloma, the EQUATE Trial. ClinicalTrials.gov. Accessed April 2024. https://clinicaltrials.gov/study/NCT04566328

97. Clinical Benefit of SAR650984, Bortezomib, Lenalidomide and Dexamethasone Combination in NDMM Patients Not Eligible for Transplant (IMROZ). ClinicalTrials.gov. Accessed April 2024. https://clinicaltrials.gov/study/NCT03319667

98. Multicenter Open Label Phase 3 Study of Isatuximab Plus Lenalidomide and Dexamethasone With/Without Bortezomib in the Treatment of Newly Diagnosed Non Frail Transplant Ineligible Multiple Myeloma Elderly Patients (≥ 65; < 80 Years). ClinicalTrials.gov. Accessed April 2024. https://clinicaltrials.gov/study/NCT04751877

99. A Study of Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Treatment in Participants With Newly Diagnosed Multiple Myeloma Who Are Minimal Residual Disease Positive After Frontline Autologous Stem Cell Transplant (AURIGA). ClinicalTrials.gov. Accessed April 2024. https://www.clinicaltrials.gov/study/NCT03901963

100. S1803, Lenalidomide +/- Daratumumab/rHuPh20 as Post-ASCT Maintenance for MM w/ MRD to Direct Therapy Duration (DRAMMATIC). ClinicalTrials.gov. Accessed April 2024. https://www.clinicaltrials.gov/study/NCT04071457

101. Post-Transplant Maintenance Therapy With Isatuximab Plus Lenalidomide for High-Risk Multiple Myeloma Patients. ClinicalTrials.gov. Accessed April 2024. https://www.clinicaltrials.gov/study/NCT05776979

102. Post-Autologous Transplant Maintenance With Isatuximab and Lenalidomide in Minimal Residual Disease Positive Multiple Myeloma (HEME-18). ClinicalTrials.gov. Accessed April 2024. https://www.clinicaltrials.gov/study/NCT05344833

103. Evaluation iNduction, Consolidation and Maintenance Treatment With Isatuximab , Carfilzomib, LEnalidomide and Dexamethasone. ClinicalTrials.gov. Accessed April 2024. https://www.clinicaltrials.gov/study/NCT03104842

104. Myeloma XIV: Frailty-adjusted Therapy in Transplant Non-Eligible Patients With Newly Diagnosed Multiple Myeloma (FiTNEss). ClinicalTrials.gov. Accessed April 2024. https://www.clinicaltrials.gov/study/NCT03720041

105. A Study to Compare Iberdomide Maintenance Versus Lenalidomide Maintenance Therapy Following Autologous Stem Cell Transplant in Participants With Newly Diagnosed Multiple Myeloma. ClinicalTrials.gov. Accessed April 2024. https://www.clinicaltrials.gov/study/NCT05827016

106. Iberdomide and Daratumumab as Maintenance Therapy After an Autologous Stem Cell Transplant for Multiple Myeloma (IBEX). ClinicalTrials.gov. Accessed April 2024. https://www.clinicaltrials.gov/study/NCT06107738

107. A Study to Compare the Efficacy and Safety of Idecabtagene Vicleucel With Lenalidomide Maintenance Therapy Versus Lenalidomide Maintenance Therapy Alone in Adult Participants With Newly Diagnosed Multiple Myeloma Who Have Suboptimal Response After Autologous Stem Cell Transplantation (KarMMa-9). ClinicalTrials.gov. Accessed April 2024. https://www.clinicaltrials.gov/study/NCT06045806

108. A Study of Bortezomib, Lenalidomide and Dexamethasone (VRd) Followed by Cilta-cel, a CAR-T Therapy Directed Against BCMA Versus VRd Followed by Lenalidomide and Dexamethasone (Rd) Therapy in Participants With Newly Diagnosed Multiple Myeloma for Whom ASCT is Not Planned as Initial Therapy (CARTITUDE-5). ClinicalTrials.gov. Accessed April 2024. https://www.clinicaltrials.gov/study/NCT04923893