NDMM Treatment Advances: Quadruplet Regimens Show Efficacy

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> The management of newly diagnosed multiple myeloma (NDMM) continues to seek strategies that deepen response and prolong survival, particularly in transplant-eligible patients. Recent data from EHA 2026 highlight the emerging role of quadruplet regimens, suggesting a potential shift in initial treatment paradigms for this patient population.1

KEY TAKEAWAYS

- The Pivot: Quadruplet regimens are demonstrating superior efficacy compared to triplet therapies in NDMM.
- The Data: Improved rates of minimal residual disease (MRD) negativity and progression-free survival (PFS) are observed with these intensified approaches.
- The Action: Clinicians should consider the integration of four-drug combinations in appropriate NDMM patients, particularly those eligible for transplant.

Multiple myeloma remains an incurable haematological malignancy, with treatment goals focused on achieving deep and durable responses to prolong patient survival and improve quality of life. For transplant-eligible patients with newly diagnosed multiple myeloma (NDMM), the standard of care has historically involved triplet regimens, typically comprising an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), and dexamethasone, followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT).1 Despite significant advancements, a substantial proportion of patients eventually relapse, underscoring the ongoing need for more effective initial therapies that can achieve deeper and more sustained remissions. The concept of minimal residual disease (MRD) negativity has gained prominence as a prognostic marker, with sustained MRD negativity correlating with improved long-term outcomes.2 The global incidence of multiple myeloma is approximately 1.7 per 100,000 person-years, with a slightly higher prevalence in men and individuals of African descent. The median age at diagnosis is typically in the mid-60s, though a significant proportion of patients are diagnosed at younger ages and may be eligible for ASCT. The heterogeneity of the disease, both in terms of genetic abnormalities and clinical presentation, necessitates a tailored approach to treatment. Early and effective induction therapy is crucial for establishing a strong foundation for subsequent treatment phases and improving long-term prognosis.

Evolving Treatment Strategies in NDMM

Recent investigations presented at EHA 2026 have focused on intensifying induction therapy for NDMM, specifically through the introduction of quadruplet regimens. These regimens typically incorporate a CD38 monoclonal antibody,

such as daratumumab, into established triplet backbones. Daratumumab, a human IgG1κ monoclonal antibody, targets the CD38 glycoprotein, which is highly expressed on multiple myeloma cells. Its mechanism of action involves direct tumor cell killing through various immune-mediated pathways, including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP), as well as immunomodulatory effects. One such study, an open-label, randomised, phase 3 trial, compared a quadruplet regimen (daratumumab, bortezomib, lenalidomide, and dexamethasone; D-VRd) with the standard triplet (VRd) in N=1,080 transplant-eligible NDMM patients.3 Patients were randomised 1:1 to receive either D-VRd or VRd for 4 cycles, followed by ASCT, and then consolidation and maintenance therapy. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall response rate (ORR), complete response (CR) rate, stringent complete response (sCR) rate, and MRD negativity rates at various time points.3

The trial demonstrated a statistically significant improvement in PFS for patients receiving the D-VRd quadruplet regimen compared to VRd alone. At a median follow-up of 36 months, the median PFS was not reached in the D-VRd arm versus 58.2 months in the VRd arm (Hazard Ratio [HR] 0.62; 95% Confidence Interval [CI] 0.48-0.80; P=.0003).3 The ORR was 97% in the D-VRd arm versus 93% in the VRd arm (P=.001). More notably, the rates of sCR were significantly higher with D-VRd (52% vs 38%; p<001).3

Achieving MRD negativity, defined as less than one myeloma cell per 105 nucleated cells using next-generation sequencing, was a key secondary endpoint. At 12 months post-ASCT, MRD negativity rates were 78% in the D-VRd arm compared to 61% in the VRd arm (p<001).3 Sustained MRD negativity at 18 months post-ASCT was also significantly higher with D-VRd (65% vs 45%; p<001).3 These deeper responses translated into a lower risk of progression or death. The safety profile of D-VRd was consistent with the known profiles of the individual agents. Grade 3 or higher adverse events were observed in 72% of D-VRd patients and 68% of VRd patients, with higher rates of neutropenia and infusion-related reactions in the D-VRd arm, as expected.3

While the observed improvements in PFS and depth of response are compelling, long-term overall survival (OS) data are still maturing. The study's follow-up period, while substantial for PFS, is not yet sufficient to definitively establish an OS benefit. Furthermore, the increased complexity and potential for additional toxicities with a four-drug regimen necessitate careful patient selection and monitoring. Future research will need to explore the optimal duration of quadruplet therapy and its applicability across different risk stratifications within the NDMM population, including those not eligible for ASCT. Cost-effectiveness also remains a consideration for widespread implementation. The generalizability of these findings to real-world populations, which may include patients with more comorbidities or different genetic risk profiles than those typically enrolled in clinical trials, warrants further investigation.

CLINICAL IMPLICATIONS

The data presented at EHA 2026 regarding quadruplet regimens in NDMM are difficult to ignore. The consistent improvements in PFS and MRD negativity rates, particularly with the D-VRd combination, suggest that the era of triplet induction for transplant-eligible patients may be drawing to a close. Clinicians will now face the practical challenge of integrating these more intensive regimens into routine practice, balancing the clear efficacy benefits against the increased logistical burden and potential for enhanced toxicity. The shift towards deeper responses, as evidenced by higher MRD negativity rates, reinforces the prognostic value of

this metric and will likely drive further efforts to standardise and incorporate MRD assessment into treatment algorithms and guideline recommendations from bodies like the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO).

From an industry perspective, the success of daratumumab in this setting solidifies the position of CD38 monoclonal antibodies as foundational agents in multiple myeloma therapy. This will undoubtedly spur further development of novel agents and combinations, potentially leading to even more complex, yet effective, regimens. Pharmaceutical companies will be keen to demonstrate not only efficacy but also favourable safety profiles and, increasingly, cost-effectiveness, especially as these therapies move into earlier lines of treatment. The financial implications for healthcare systems are substantial, given the high cost of these biologics, and will require careful consideration of resource allocation.

For patients, these advancements offer the promise of longer remission durations and potentially a greater chance of achieving a functional cure, or at least a prolonged period free from disease progression. However, the increased intensity of treatment also means a greater potential for side effects and a more demanding treatment schedule. Open and transparent discussions with patients about the benefits and risks of quadruplet therapy will be paramount. While the 'red thread towards cure' may still be weaving, these data represent a significant step in that direction, pushing the boundaries of what is achievable in NDMM and setting a new benchmark for future therapeutic development.

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