About the Authors

Rina Latscha, MD

Dr. Rina Latscha is a Clinical Research Fellow in the Lymphoma, Myeloma and Transplant Program at the Princess Margaret Cancer Centre in Toronto. She completed medical school in Hamburg, Germany, and is board-certified in Internal Medicine and Hematology, with specialist training in Switzerland. Her work focuses on patient-centered clinical research, as well as medical education and curriculum development across the healthcare continuum, including nurses, trainees, residents, fellows, patients, and caregivers.

Affiliations: Department of Medical Oncology Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Sita Bhella, MD

Dr. Sita Bhella is a staff hematologist at Princess Margaret Cancer Centre. She specializes in malignant hematology, with a primary clinical focus on lymphoma, myeloma, autologous stem cell transplantation and cellular t therapies. She is an Assistant Professor within the Department of Medicine at the University of Toronto and is the Autologous Stem Cell Transplant Medical Director at Princess Margaret Cancer Centre.

Affiliations: Department of Medical Oncology Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

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Upfront Therapy for Non-transplantable Multiple Myeloma in 2026: Decision-making in an Increasingly Complex Therapeutic Landscape

Rina Latscha, MD
Sita Bhella, MD

Introduction

Multiple myeloma (MM) is an age-related disease with a median age at diagnosis of approximately 70 years.[1] While quadruplet regimens, such as daratumumab, bortezomib, lenalidomide, and dexamethasone (Dara-VRd), followed by autologous hematopoietic stem cell transplantation (HSCT), as demonstrated in the Perseus trial, have recently become a standard for transplant-eligible patients, optimal first-line therapy remains challenging in older, frail individuals with comorbidities and reduced functional reserve. This challenge is driven less by biological differences in the disease and more by heterogeneity in treatment tolerance, comorbidity burden, and real-world care conditions.[1-3]

Historically, non-transplant-eligible patients were treated with doublets, such as melphalan/prednisone or lenalidomide/dexamethasone (Rd). With the introduction of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs), triplet regimens, including VRd and later DRd (daratumumab, lenalidomide, dexamethasone), became the new standard of therapy.[1,2]

A major advance was the incorporation of monoclonal CD38 antibodies. Network meta-analyses have shown that anti-CD38 monoclonal antibody-based combinations significantly improve progression-free survival (PFS) and response rates compared with regimens lacking anti-CD38 therapy.[4] However, increasing efficacy has also led to greater treatment complexity and toxicity, which is particularly relevant for older and frail patients.

For this population, first-line therapy must balance effective disease control with minimizing treatment-related morbidity and preserving quality of life. In addition, regional differences in access to modern therapies—especially to anti-CD38 monoclonal antibodies and quadruplet combinations—further widen the gap between evidence-based recommendations and real-world practice.[3]

This review provides practical guidance on selecting first-line therapy for patients with MM who are not eligible for transplantation, focusing on efficacy, toxicity profiles, and key clinical decision factors.

What Role Does Frailty Play in Choosing First-line Therapy?

Although age was once the main determinant of treatment decisions, this paradigm has shifted substantially. A landmark International Myeloma Working Group (IMWG) analysis identified frailty as an independent predictor of mortality, treatment discontinuation, and severe adverse events. The three-year overall survival (OS) was 84% in fit patients but declined to 57% in frail individuals.[5]

A systematic review further confirmed that geriatric impairments—particularly in mobility, cognition, polypharmacy, and activities of daily living—are associated with higher mortality, increased toxicity, and reduced treatment feasibility.[6]

While the IMWG frailty score is the most extensively validated tool, its complexity limits routine use. Simplified models incorporating age, Eastern Cooperative Oncology Group (ECOG) performance status, and comorbidities show comparable prognostic value and greater clinical practicality.[5,7-9]

Frailty is also increasingly viewed as a dynamic concept. Integrating geriatric

assessment with hematopoietic parameters improves prediction of treatment-related toxicities and underscores the need for repeated frailty evaluation throughout therapy, not only at baseline.[10] This is particularly relevant with modern continuous treatment strategies, as functional status may improve or deteriorate over time (**Table 1**).

Which Patients Benefit from Quadruplet Regimens?

The introduction of quadruplet regimens represents a major advance in MM therapy, enabling deeper remissions and more durable disease control than established triplets (**Table 2**). This is particularly relevant for transplant-ineligible patients, as a substantial proportion will not receive second- or third-line therapy during their disease course.[11] Consequently, the effectiveness of first-line treatment has a disproportionate impact on long-term prognosis.

The phase III CEPHEUS trial compared Dara-VRd with VRd in patients unsuitable for or deferring transplantation, demonstrating a significant 43% reduction in the risk of progression or death (hazard ratio [HR]: 0.57). The remission depth was markedly improved, with minimal residual disease (MRD)-negativity rates of 60.9% versus 39.4% in favour of the quadruplet. These findings support Dara-VRd as a potential new standard for functionally fit patients without immediate transplant intent. However, higher rates of hematologic toxicity were observed, particularly grade 3/4 neutropenia (44.2% vs. 29.7%), and pneumonia was the most frequent serious adverse event (13.7% vs. 12.8%). Importantly, discontinuation due to toxicity remained lower with Dara-VRd than with VRd alone (7.6% vs. 15.9%), indicating overall feasibility in selected patients.[12]

Similar results were reported in the IMROZ study, which evaluated Isa-VRd (isatuximab, bortezomib, lenalidomide, dexamethasone) versus VRd in transplant-ineligible patients. After nearly five years of follow-up, the estimated 60-month PFS rate was 63.2%, compared with 45.2%, respectively, corresponding to a 40% risk reduction (HR: 0.60). Higher complete response and MRD-negativity rates were also achieved. As with other quadruplet therapies, this benefit came at the cost of increased toxicity, including higher rates of severe infections (grade ≥3: 44.9% vs. 38.1%) and grade 3/4 neutropenia (54.4% vs. 37.0%). Notably, infection rates were lower in patients receiving antibiotic prophylaxis, underscoring the importance of supportive measures.[13]

Peripheral neuropathy remains a key limitation of bortezomib-based quadruplets. In the French BENEFIT study comparing Isa-VRd with Isa-Rd, neuropathy occurred in 52% of Isa-VRd-treated patients, with 27% having grade ≥2 neuropathy. Ten percent discontinued bortezomib due to neurologic toxicity, highlighting the need for caution in patients with pre-existing neuropathy or diabetic comorbidities.[14]

Renal dysfunction represents another important clinical scenario, as lenalidomide-based regimens often require dose reduction or delay. In this context, bortezomib/cyclophosphamide-based quadruplets provide an alternative. The Dara-VCD (Dara-CyBorD; daratumumab, cyclophosphamide, bortezomib, dexamethasone) study demonstrated that weekly bortezomib was tolerable in elderly and frail patients, with peripheral neuropathy rates of only 28% and no grade 3/4 events. Infections, particularly upper respiratory tract infections and pneumonia, were more frequent with daratumumab, emphasizing the need for close monitoring. Dara-VCD may therefore be particularly attractive in renal myeloma requiring rapid cytoreduction.[15]

Beyond PI/IMiD-based approaches, alkylator-containing quadruplets remain clinically relevant, particularly for very elderly patients or those with renal impairment. In the ALCYONE trial, Dara-VMP (daratumumab, bortezomib, melphalan, prednisone) significantly improved OS compared with VMP alone (83.0 vs. 53.6 months; HR: 0.65). Approximately one-third of participants were aged ≥75 years, supporting applicability in older populations. Severe neutropenia occurred in ~40% of patients, and infections were more frequent, although discontinuation rates remained below 10%, suggesting feasibility with appropriate geriatric assessment.[16,17]

Which Patients Benefit from Triplet Regimens?

Quadruplet regimens are mainly reserved for functionally fit patients with the goal of achieving the deepest possible remission, while triplet therapies remain more appropriate for many transplant-ineligible individuals. Triplets provide substantially improved disease control compared with doublets, without the added toxicity burden associated with four-drug combinations.

Consequently, they often represent the most pragmatic first-line option for a large proportion of patients with non-transplant-eligible myeloma.

The phase III MAIA trial established DRd as a reference regimen in this setting. After a median follow-up of more than five years, DRd significantly prolonged PFS compared with Rd alone (median 61.9 vs. 34.4 months; HR: 0.55) and also conferred an OS advantage (HR: 0.66). Importantly, this benefit was consistent across all age groups, including patients aged ≥80 years, in whom the PFS improvement remained substantial (HR: 0.48).[18] These results explain why DRd is widely regarded as the preferred triplet for many transplant-ineligible patients in routine practice.

However, the MAIA study also highlighted that increased efficacy may be accompanied by higher rates of infections and cytopenias. While treatment discontinuation due to adverse events was lower with DRd than with Rd (15.7% vs. 24.4%), careful monitoring remains essential, particularly in more vulnerable patients.[18]

Beyond anti- CD38 monoclonal antibody-based triplets, the proteasome inhibitor/IMiD-based VRd regimen remains a key cornerstone of first-line therapy. In the randomized phase III SWOG S0777 trial, VRd significantly improved both PFS (41 vs. 29 months; HR: 0.74) and OS (not reached vs. 69 months; HR: 0.71) compared with Rd. This benefit persisted after adjustment for age, confirming the effectiveness of VRd beyond the transplant population.[19]

Nevertheless, full-dose VRd is not always feasible in older patients, largely due to cumulative neuropathy toxicity. This underscores the importance of frailty-adapted approaches in optimizing triplet therapy for less robust individuals.

Frailty-adapted Triplets: VRd-lite and Dexamethasone Reduction: A Bridge Between Intensity and Tolerability

VRd-lite represents a particularly relevant option for the large group of intermediately fit patients who are too vulnerable for quadruplets yet too resilient for doublet therapy. This dose-adapted regimen was designed to preserve the efficacy of a proteasome inhibitor–based triplet while substantially reducing toxicity.

In the phase II RVD lite study, median PFS reached 35.1 months, with a very low incidence of severe neuropathy (grade ≥3: 2%). Most neuropathic symptoms remained mild, underscoring the clinical attractiveness of this approach in older patients.[20] VRd-lite therefore provides an important balance between efficacy and tolerability, especially for individuals who require PI-based therapy but cannot tolerate full-dose VRd.

Another key insight in optimizing triplet therapy is the recognition that both drug selection and steroid exposure strongly influence tolerability. In frail patients, steroid-related toxicities—including delirium, muscle weakness, hyperglycemia, and infections—are often the primary limiting factor.

In this context, the phase III IFM2017-03 trial is particularly practice-changing. Conducted in a frail population with a median age of 81 years, it evaluated a dexamethasone-sparing regimen of daratumumab and lenalidomide, with dexamethasone restricted to the first two cycles only. This strategy significantly prolonged PFS compared with standard Rd (53.4 vs. 22.5 months; HR: 0.51), without additional safety concerns.[21]

These findings demonstrate that frailty-adapted de-escalation does not necessarily compromise efficacy but may instead improve long-term treatment feasibility. For vulnerable patients, reducing steroid intensity can, therefore, translate into meaningful clinical benefit, marking an important shift toward more individualized first-line strategies.

Will Rd Still be Relevant in 2026?

In an era of highly effective CD38-based triplet and quadruplet regimens, classic doublets such as lenalidomide and dexamethasone (Rd) may appear largely outdated. Indeed, the first-line standard for transplant-ineligible patients has evolved substantially. Nevertheless, Rd remains clinically relevant—not as the default option, but within a clearly defined, patient-centred context.

The historical role of Rd is largely based on the pivotal phase III FIRST trial, which compared Rd with melphalan-based regimens. Rd significantly prolonged OS versus MPT (melphalan, prednisone, thalidomide; median OS 59.1 vs. 49.1 months; HR: 0.78), establishing it as a long-standing standard for non-transplant-eligible patients. Importantly, long-term follow-up revealed no new safety concerns.[22]

Frailty Tool / Approach	Key Components	Clinical Output	Strengths	Limitations	Practical Use in First-line Decision-Making
IMWG Frailty Index[5]	Age (≤75, 76-80, >80 years); Charlson Comorbidity Index (CCI ≤1 or ≥2); ADL (>4 or ≤4); IADL (>5 or ≤5)	Score 0-5: Fit (0), Intermediate (1), Frail (≥2)	Most widely validated in MM; predicts OS, PFS, toxicity, and treatment discontinuation; 3-year OS: fit 84-91%, intermediate 74-77%, frail 47–57%; online calculator available	Requires ADL/IADL assessment not routinely collected; heavily weighs age (no fit patients >75 years); time-consuming in busy clinics; limited ability to distinguish toxicity risk between fit and intermediate-fit patients	Gold standard for MM frailty assessment; guides treatment intensity and dose modifications
Simplified Frailty Scale (ECOG-based)[7]	Age; CCI; ECOG PS	Frail vs. non-frail classification	Easy to implement using readily available clinical data; validated in FIRST trial; predicts OS, PFS, and grade 3/4 AEs; improves prognostic assessment when combined with ISS	Less granular than IMWG (2 vs. 3 categories); may miss nuanced functional impairments	Most user-friendly for daily practice; can be calculated immediately at bedside; useful for rapid treatment stratification
Revised Myeloma Comorbidity Index (R-MCI)[8]	Renal, lung, and Karnofsky performance impairment; age; cytogenetics	Risk stratification for fit vs. frail	Strong prognostic value for OS and PFS; 3-year OS differences: fit 90%, intermediate 74%, frail 43%; complements IMWG score; superior to age-based subgroups for treatment tailoring	Requires cytogenetic data, which may delay assessment; more complex scoring	Useful when cytogenetic data are available; particularly valuable for comprehensive risk stratification combining disease and patient factors; guides initial dose reduction decisions
Hemo-IMWG GA (Combined Model)[10]	IMWG GA components plus HS: hemoglobin, platelet count, absolute neutrophil count	Dynamic frailty assessment with integrated hematologic risk	Superior predictive performance for total toxicity (C-index 0.615) and non-hematological toxicity (C-index 0.605); HS strongly stratifies hematological AEs (HR=9.91); allows dynamic reassessment across treatment cycles	Requires serial assessment; more complex than single-timepoint tools; relatively new with limited external validation	Optimizes prediction of chemotherapy tolerance by combining functional and hematopoietic dimensions; particularly useful for predicting hematological toxicity; enables personalized treatment adjustments during therapy

Frailty Tool / Approach	Key Components	Clinical Output	Strengths	Limitations	Practical Use in First-line Decision-Making
G8 Questionnaire[9]	8 items derived from Mini Nutritional Assessment	Score 0–17; ≤14 abnormal	Widely validated across cancers including hematologic malignancies; high sensitivity (73-81%); quick screening tool; predicts survival, treatment tolerance, hospitalization	Lower specificity (44–80%); screening tool, not comprehensive assessment	First-line screening to identify who needs full GA; takes 5 minutes; recommended by NCCN for older adults with cancer; validated in hematology populations
Vulnerable Elders Survey-13 (VES-13)[9]	13 self-reported items on age, self-rated health, physical function, ADL	Score 1–10; ≥3 vulnerable	Self-administered in 5 minutes; high specificity (70-100%); predicts survival, toxicity, treatment tolerance	Lower sensitivity (46–69%) vs. G8; may miss some vulnerable patients	Efficient self-administered screening; useful when staff time is limited; validated for treatment outcome prediction in hematology

Table 1. Validated frailty assessment tools used in transplant-ineligible patients with newly-diagnosed multiple myeloma, outlining key components and their implications for first-line treatment selection; *courtesy of Rina Latscha, MD and Sita Bhella, MD*.

Frailty classification (fit, intermediate, frail, or vulnerable) predicts survival, treatment-related toxicity, and feasibility of therapy intensity.

Abbreviations: ADL: Activities of Daily Living; **AEs:** adverse events; **CCI:** Charlson Comorbidity Index; **ECOG PS:** Eastern Cooperative Oncology Group Performance Status; **GA:** Geriatric Assessment; **HS:** Hematopoietic Score; **IADL:** Instrumental Activities of Daily Living; **IMWG:** International Myeloma Working Group; **ISS:** International Staging System; **MM:** multiple myeloma; **NCCN:** National Comprehensive Cancer Network; **OS:** overall survival; **PFS:** progression-free survival; **R-MCI:** Revised Myeloma Comorbidity Index.

Study	Study Type	Population	Treatment	Response Rate	PFS	OS	Key Toxicity
CEPHEUS[12]	Phase III, randomized	Transplant-ineligible or transplant-deferred NDMM (n=395)	D-VRd vs. VRd (8 cycles) followed by D-Rd or Rd	≥CR: 81.2% vs. 61.6%; MRD-neg: 60.9% vs. 39.4%	Median not reached vs. NR; HR: 0.57 (95% CI 0.41-0.79)	Median follow-up 58.7 months; OS data immature	Higher neutropenia, thrombocytopenia, peripheral neuropathy; but consistent with known safety profiles
IMROZ[13]	Phase III, randomized	Transplant-ineligible NDMM, age 18–80 (n=446)	Isa-VRd vs. VRd (3:2 randomization	≥CR: 74.7% vs. 64.1%; MRD-neg + CR: 55.5% vs. 40.9%	60-month PFS: 63.2% vs. 45.2%; HR: 0.60 (98.5% CI: 0.41-0.88)	Median follow-up 59.7 months; OS data immature	Neutropenia (54.4% vs. 37.0% grade ≥3), infections (44.9% vs. 38.1%; grade ≥3); no new safety signals
BENEFIT[14]	Phase III, randomized	TI NDMM age 65–79 (n=270)	Isa-VRd (12 cycles) followed by Isa-Rd vs. Isa-Rd	≥CR: 65.4% vs. 47.1% (p=0.002); MRD-neg (10^{-5}): 53.6% vs. 26.8%; Sustained MRD-neg ≥12 months: 42.5% vs. 18.3%	Median: Not reached vs 47.0 months; HR 0.54 (95% CI: 0.36–0.81, p=0.003);	Median follow-up: 42.5 months; OS data immature; HR 0.75 (95% CI 0.44–1.28, p=0.29)	Neutropenia: 50.3% vs. 39.9% (grade ≥3); infections: 50.3% vs. 48.4% (any grade), 22.2% vs. 19.6% (grade ≥3); peripheral neuropathy: 44.4% vs. 26.8% (any grade), 3.3% vs. 0.7% (grade ≥3);
ALCYONE[16]	Phase III, randomized	TI NDMM ≥65 or comorbidities (n=706)	D-VMP vs. VMP	≥CR: 42.6% vs. 24.4%; MRD-neg: 22.3% vs. 6.2%	Median 18.1 months (primary); HR: 0.50 (95% CI: 0.38-0.65)	Median 83.0 vs 53.6 months; HR 0.65 (95% CI 0.53–0.80) at 86.7 months follow-up	Neutropenia (40% vs. 39% grade 3/4), thrombocytopenia (35% vs. 38%), anemia (18% vs. 20%)
AMaRC3-16[15]	Phase II/III randomized	TI NDMM (n=121)	D-VCD vs. VCD	ORR: 86% vs. 65% (p=0.007); ≥VGPR: 52% vs. 28% (p=0.009)	25.8 months (95% CI: 19.9-33.5) vs. 16.8 months (95% CI: 15.3-21.7); HR: 0.67; PFS 30 months: 41% vs. 27% (p=0.0001)	Not reported in final analysis	72% completed 9 cycles of induction; no grade 3/4 peripheral neuropathy; well tolerated with no new safety signals
MAIA[18]	Phase III, randomized	TI NDMM (n=737)	D-Rd vs. Rd	≥CR: 51.1% vs. 30.1%; MRD-neg: 32.1% vs. 11.1%	Median 61.9 vs. 34.4 months; HR: 0.55 (95% CI: 0.45-0.67)	Median NR vs. 65.5 months; HR: 0.66 (95% CI: 0.53-0.83) at 64.5 months follow-up	Neutropenia (54% vs. 37% grade ≥3), pneumonia (19% vs. 11%), anemia (17% vs. 22%)

Study	Study Type	Population	Treatment	Response Rate	PFS	OS	Key Toxicity
SWOGS0777[19]	Phase III, randomized	NDMM without intent for early ASCT (n=460)	VRd (8 cycles) vs. Rd (6 cycles) followed by Rd maintenance	≥CR: 15.7% vs. 8.4%; ORR: 82% vs. 72%	Median 43 vs. 30 months; HR: 0.712 (96% CI: 0.56–0.906)	Median 75 vs. 64 months; HR: 0.709 (95% CI: 0.524–0.959)	Neuropathy risk increased with bortezomib Grade ≥3 AEs: 82% vs. 75%; discontinuation due to AEs: 23% vs. 10%
RVD-lite[20]	Phase II, single-arm	TI NDMM (n=50)	Modified RVd: R 15mg days 1–21, V 1.3mg/m² weekly SC, D 20mg (35-day cycles)	ORR: 86%; ≥VGPR: 66%	Median 35.1 months (95% CI: 30.9–NR)	Median not reached at 30 months follow-up	Peripheral neuropathy: 62% (only 1 grade 3); well-tolerated
IFM2017-03[21]	Phase III, randomized	Frail NDMM, age ≥65 years, ECOG frailty score ≥2 (n=295)	D-Rd (dex only 2 cycles) vs. Rd (2:1 randomization	≥CR: 47.5% vs. 28.4%; MRD-neg at 12 months: 24% vs. 9%	Median 53.4 vs. 22.5 months; HR: 0.51 (95% CI: 0.37–0.70)	Median follow-up 46.3 months; OS data immature	Neutropenia (55% vs. 24% grade 3–5), infections (19% vs. 21%); serious AEs: 63% vs. 69%
FIRST Trial[22]	Phase III, randomized	TI NDMM (n=1623)	Rd continuous vs. Rd18 vs. MPT (72 weeks)	≥CR: higher with Rd continuous vs MPT	Median 26 vs. 21 vs. 21 months (Rd continuous vs. Rd18 vs. MPT); HR: 0.69 vs. MPT	Median 59.1 vs. 62.3 vs. 49.1 months (Rd continuous vs. Rd18 vs. MPT); HR: 0.78 vs. MPT	No new safety concerns; no increased risk of secondary malignancies; steroid-related AEs relevant in elderly

Table 2. Major clinical trials evaluating modern CD38 antibody–based quadruplet and triplet regimens in transplant-ineligible or transplant-deferred patients with newly diagnosed multiple myeloma; *courtesy of Rina Latscha, MD and Sita Bhella, MD.*

Reported outcomes include depth of response, PFS, OS, and key treatment-related toxicities. These data highlight the balance between improved efficacy with intensified regimens and the increased risk of hematologic and infectious adverse events in older or frail populations.

Abbreviations: AEs: adverse events; **ASCT:** autologous stem cell transplant; **CI:** confidence interval; **CR:** complete response; **D-Rd:** daratumumab + lenalidomide + dexamethasone; D-VCD: daratumumab + bortezomib + cyclophosphamide + dexamethasone; **D-VMP:** daratumumab + bortezomib + melphalan + prednisone; **D-VRd:** daratumumab + bortezomib + lenalidomide + dexamethasone; **HR:** hazard ratio; **Isa-VRd:** isatuximab + bortezomib + lenalidomide + dexamethasone; **MPT:** melphalan + prednisone + thalidomide; **MRD-neg:** minimal residual disease negativity; **NDMM:** newly-diagnosed multiple myeloma; **NR:** not reached; **ORR:** overall response rate; **OS:** overall survival; **PFS:** progression-free survival; Rd: lenalidomide + dexamethasone; RVd: lenalidomide + bortezomib + dexamethasone; **TI:** transplant-ineligible; **VGPR:** very good partial response; **VCD:** bortezomib + cyclophosphamide + dexamethasone; **VRd:** bortezomib + lenalidomide + dexamethasone.

With the incorporation of daratumumab into first-line therapy, Rd has increasingly served as the control arm in modern trials. As expected, it was clearly inferior to DRd in the MAIA study, yet still achieved a median OS of 65.5 months. This highlights that less intensive therapy can provide durable disease control, particularly in patients able to tolerate continuous treatment.[18]

Therefore, the key issue is not maximal efficacy alone, but the appropriateness of treatment intensity. For some individuals—especially very frail older patients with limited physiological reserve, significant comorbidity burden, or restricted life expectancy—continuous triplet therapy may be impractical despite its benefits. In such cases, Rd remains an important alternative due to its outpatient administration, oral convenience, and manageable toxicity profile, while prioritizing quality of life and patient autonomy.

Side Effects as a Key Tool for Managing Treatment

For patients who are not eligible for transplantation, first-line therapy for MM will be less a purely regimen-based decision and increasingly a question of treatment feasibility under real geriatric conditions. Although quadruplet and triplet regimens can significantly prolong PFS, clinical practice remains characterized by a persistent tension between efficacy and toxicity. As treatment intensity increases, so does the overall toxicity burden, which often limits therapy in older patients.[3]

Hematological toxicities, such as neutropenia and thrombocytopenia, as well as the resulting hospitalizations, are particularly relevant because they are not merely adverse events but often mark the beginning of functional decline. Infections in older patients can rapidly lead to loss of mobility, delirium, or the need for nursing care—outcomes that are not adequately captured by traditional trial endpoints.

RRMM=relapsed or refractory multiple myeloma; CD38=cluster of differentiation 38; CI=confidence interval; NE=non estimable; SC=subcutaneous(ly); q2w=every 2 weeks; IRC=Independent Review Committee; IMWG=International Myeloma Working Group.

* Comparative clinical significance unknown.

† Phase 1/2, single-arm, open-label, multicentre study in adults with RRMM who had received ≥3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. Patients received initial step-up doses of 0.06 mg/kg and 0.3 mg/kg administered SC, followed by 1.5 mg/kg SC once-weekly thereafter until disease progression or unacceptable toxicity. Patients who had a CR or better for ≥6 months were eligible to reduce dosing frequency to 1.5 mg/kg SC q2w until disease progression or unacceptable toxicity. Efficacy population treated at the pivotal study dose in phase 2 had a median duration of follow-up of 8.8 months at the primary analysis.

‡ ORR was a composite of sCR + CR + VGPR + PR as determined by the IRC assessment using IMWG 2016 criteria.

§ Follow-up analysis included 15 additional patients since the primary analysis.

¶ Efficacy population treated at the pivotal dose in phase 2.

** Clinical significance unknown.

†† Based on sales data (up to August 31, 2025), it is estimated that approximately 19,177 patients have been exposed to teclistamab in the post-marketing setting. An estimated total of 2,821 participants were exposed to teclistamab in the Company-sponsored and collaborative interventional clinical trials.[3]

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- ICANS, including fatal outcome, occurred in post-marketing experience
- Potential for immunogenicity

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The Product Monograph is also available by calling 1-800-567-3331.

References: 1. TECVAYLI® (teclistamab injection) Product Monograph. Janssen Inc. June 26, 2025. **2.** Data on file, Johnson & Johnson. October 13, 2023. **3.** Data on file, Johnson & Johnson. October 31, 2025.

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Another frequently underestimated factor is steroid-associated toxicity. Dexamethasone remains part of many standard regimens, yet its side effects—including sleep disturbances, delirium, muscle weakness, hyperglycemia, and an increased risk of falls—are highly clinically relevant in geriatric patients. Reviews of treatment in older myeloma populations emphasize that steroid toxicity is often underestimated, despite its major contribution to treatment discontinuation rates.[10]

A substantial proportion of patients present with impaired renal function at diagnosis. The IMWG highlights that up to 50% of patients with myeloma have renal involvement, which is associated with higher early mortality and poorer OS. This has direct therapeutic implications: bortezomib-based regimens remain the cornerstone of treatment in this setting, as they induce rapid responses and improve the likelihood of renal recovery.[23]

Beyond renal impairment, individual neuropathy risk is another decisive factor. Although bortezomib-containing regimens such as VRd or VRd-based quadruplets are highly effective, they may cause peripheral neuropathy with a substantial impact on quality of life in older patients. The *American Society of Clinical Oncology (ASCO)–Ontario Health Living Guideline* therefore emphasizes that, outside of emergency situations, twice-weekly bortezomib should be avoided, as weekly administration provides comparable efficacy with significantly lower neuropathy rates.[23]

Patients with pre-existing polyneuropathy, diabetes, or a tendency to fall often benefit from PI-free strategies, such as DRd or Rd. However, in aggressive disease or in the presence of renal involvement, the benefits of including a PI may outweigh the neuropathy risk.

Conclusion

First-line therapy for transplant-ineligible MM has fundamentally evolved and is now characterized by substantial therapeutic diversity. Anti-CD38 monoclonal-based triplet and quadruplet regimens have significantly improved PFS and, in several studies, OS. As a result, even older patients can achieve long-term disease control to an extent previously observed mainly in transplant-eligible populations.

However, these advances have also increased clinical complexity. Treatment decisions are no longer driven solely by maximal efficacy, but by the question of which regimen is feasible, safe, and sustainable for an individual patient. In transplant-ineligible patients, treatment tolerance is often the primary limiting factor rather than lack of therapeutic effectiveness.

Frailty has, therefore, become a central guiding principle. Geriatric assessment–based classifications (fit, intermediate, frail) predict survival, treatment discontinuation, and therapy-related toxicity more accurately than age or ECOG status alone. Impairments in daily functioning, cognition, or nutritional status strongly correlate with infection risk, mortality, and reduced treatment feasibility, even in patients with preserved performance status. Dynamic frailty models, such as the integration of IMWG geriatric assessment with hematopoietic scoring, further improve the prediction of severe adverse events and support adaptive treatment strategies over time.

Consequently, first-line decisions must systematically incorporate multiple dimensions, including frailty, comorbidities, organ function, neuropathy risk, infection vulnerability, and the practicality of continuous regimens. In this population, adverse events are not merely side effects but often determine whether therapy can be delivered effectively.

Overall, first-line treatment of transplant-ineligible myeloma requires a structured, pragmatic, and patient-centred approach. The key lies not in a universal standard regimen, but in individualized adjustment of treatment choice and intensity, with regular reassessment throughout the disease course.

Correspondence

Rina Latscha, MD
Email: rina.latscha@uhn.ca

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