Treatment Intensity in the Frontline Setting for Transplant-Ineligible Patients With Multiple Myeloma

MARK DAVIS, PA-C, DMSc (candidate)

From Texas Oncology, Fort Worth, Texas

Author's disclosure of conflicts of interest is found at the end of this article.

Correspondence to: Mark Davis, Texas Oncology, 6500 Harris Parkway, Fort Worth, TX 76132

E-mail: mark.davis@usoncology.com

https://doi.org/10.6004/jadpro.2026.17.7.14

Abstract

The management of newly diagnosed transplant-ineligible multiple myeloma remains challenging, largely because frailty complicates treatment decisions and frequently leads to the exclusion of frail patients from pivotal clinical trials. Recent subgroup analyses provide useful insight into whether quadruplet therapy may offer advantages over triplet therapy in this population. Data from the IMROZ and CEPHEUS trials were reviewed to compare outcomes between quadruplet and triplet regimens in both the overall intent-to-treat cohorts and the frailty-defined subgroups. Frailty was assessed using the International Myeloma Working Group (IMWG) frailty index in CEPHEUS and the simplified IMWG frailty score in IMROZ. Across both trials, patients with impaired performance status receiving quadruplet therapy demonstrated longer progression-free survival and higher rates of minimal residual disease negativity compared with those receiving triplet therapy. These findings suggest that quadruplet regimens may provide meaningful clinical benefit even among selected frail patients when treatment decisions are guided by comprehensive frailty assessment and individualized clinical judgment. Additional real-world evidence is needed to confirm tolerability, optimize patient selection, and further clarify the role of quadruplet therapy in this vulnerable population.

Multiple myeloma (MM) is a clonal plasma cell malignancy characterized by bone marrow infiltration, end-organ damage, and a relapsing–remitting disease course. Approaches to MM are dependent on disease state and risk factors. Active MM is defined according to the IMWG diagnostic criteria, requiring either ≥ 10% clonal bone marrow plasma cells or a biopsy-proven plasmacytoma in the presence of at least one myeloma-defining event. Myeloma-defining events include traditional CRAB features (hypercalcemia, renal insufficiency, anemia, or lytic bone disease)

or high-risk biomarkers collectively known as the SLiM criteria: ≥ 60% clonal bone marrow plasma cells; an involved-to-uninvolved serum free light chain ratio ≥ 100 with an involved free light chain concentration ≥ 100 mg/L; or more than one focal lesion measuring ≥ 5 mm on whole-body MRI. Patients who do not meet these criteria are classified as having smoldering MM or monoclonal gammopathy of undetermined significance (National Comprehensive Cancer Network [NCCN], 2025).

For decades, patient outcomes with active MM improved minimally until 2004, when the introduction of novel agents such as proteasome inhibitors and immunomodulatory drugs transformed the treatment landscape. Since that time, therapeutic advances, including monoclonal antibodies targeting CD38, bispecific antibodies directed at B-cell maturation antigen (BCMA) and G protein–coupled receptor family C group 5 member D (GPRC5D), and chimeric antigen receptor T-cell therapy, have significantly deepened treatment responses and improved overall survival.

These advances have translated into markedly improved response rates and extended median overall survival from approximately 3 years two decades ago to more than 8 to 10 years for many patients with newly diagnosed disease (Kaplan, 2022). While the introduction of novel therapies has been pivotal, the most consistent change in frontline management during this period has been the intensification of therapy from doublet to triplet and now quadruplet regimens to achieve deeper and more durable responses. Increased treatment intensity has impacted both transplant-eligible and ineligible patients. Current NCCN Guidelines designate quadruplet therapy for transplant-ineligible patients as a Category 1–preferred recommendation, using either daratumumab (Darzalex; as studied in the CEPHEUS trial) or isatuximab (Sarclisa; as studied in the IMROZ trial) in combination with lenalidomide, bortezomib, and dexamethasone (NCCN, 2025).

As the US population ages, the proportion of newly diagnosed MM patients who are older, frail, or medically complex continues to increase. Approximately 40% of patients are aged 75 years or older at diagnosis, and the burden of comorbidities, such as renal impairment, diabetes, and cardiovascular disease, significantly influences treatment feasibility (Moore et al., 2023). These demographic trends underscore the importance of treatment strategies that balance efficacy with real-world tolerability, particularly as older adults represent a growing share of the MM population.

METHODS DESCRIPTION: IMROZ AND CEPHEUS TRIALS

The IMROZ and CEPHEUS trials both evaluated quadruplet regimens in newly diagnosed MM, but the study populations differed. IMROZ enrolled only patients who were ineligible for autologous stem cell transplantation (ASCT) and evaluated isatuximab combined with bortezomib, lenalidomide, and dexamethasone (Isa-VRd) compared with VRd in this strictly transplant-ineligible population. In contrast, CEPHEUS included a broader frontline population consisting of patients who were either transplant-ineligible or eligible but deferred ASCT as initial therapy, evaluating daratumumab-VRd (D-VRd) vs. VRd. Consequently, the IMROZ results reflect outcomes specifically in a transplant-ineligible cohort, whereas CEPHEUS represents a broader frontline population that included primarily transplant-ineligible patients as well as patients who deferred ASCT; notably, 27% of patients in each treatment arm (daratumumab-VRd and VRd) had ASCT deferred (Usmani et al., 2025).

In addition, enrollment criteria differed between the studies, with eligibility based on frailty in CEPHEUS and performance status in IMROZ. While the trials shared several exclusion criteria, others differed. Exclusion criteria present in one or both studies included advanced age (≥ 80 years); Eastern Cooperative Oncology Group (ECOG) performance status > 2; estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2; grade ≥ 2 peripheral neuropathy or neuropathic pain as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5; receipt of palliative radiation therapy within 2 weeks of randomization; severe chronic obstructive pulmonary disease; moderate-to-severe asthma; a recent diagnosis of a malignancy other than MM; untreated hepatitis C infection; active hepatitis B infection; and uncontrolled diabetes mellitus (Usmani et al., 2025; Manier et al., 2025).

Both IMROZ and CEPHEUS were phase III, randomized clinical trials comparing CD38-based quadruplet therapy with standard triplet therapy VRd in patients with newly diagnosed MM. In each study and across all treatment arms, bortezomib was administered for a fixed duration and discontinued after 6 months of therapy, after which patients continued lenalidomide-based treatment with ongoing CD38 monoclonal antibody therapy, when applicable, per protocol (Usmani et al., 2025; Manier et al., 2025).

In CEPHEUS, the primary endpoint was the minimal residual disease (MRD) negativity rate at 10^{-5} sensitivity, assessed using next-generation sequencing. Secondary endpoints included overall complete response or better, progression-free survival (PFS), and sustained MRD for 12 months or longer. Frailty was determined using the original IMWG Frailty Scoring System, classifying patients as fit, intermediate-fit, or frail based on age, Charlson Comorbidity Index, Activities of Daily Living, and Instrumental Activities of Daily Living. Subgroup analyses compared frailty categories with respect to treatment efficacy, safety, and regimen intensity (Usmani et al., 2025).

In IMROZ, the primary endpoint was PFS, with secondary endpoints evaluating IMWG frailty score, which incorporates age, Charlson Comorbidity Index, and ECOG performance status to classify patients as non-frail or frail. Subgroup analyses examined outcomes by frailty status and treatment regimen (triplet vs. quadruplet therapy; Manier et al., 2025; Table 1).

RESULTS

Efficacy

The IMROZ trial established quadruplet therapy as a new benchmark in the frontline, transplant-ineligible setting. Isatuximab, bortezomib, lenalidomide, and dexamethasone (Isa-VRd) achieved a 60-month PFS of 63.2% compared with 45.2% with VRd alone (hazard ratio [HR], 0.60; 98.5% confidence interval [CI] = 0.41–0.88; $p < .001$; Facon et al., 2024). Sustained MRD negativity for 12 months was also higher with Isa-VRd (47% vs. 24%; odds ratio [OR], 2.70; 95% CI = 1.80–4.14) in the intent-to-treat patient population (Facon et al., 2024). Using the simplified IMWG (sIMWG) score, at enrollment, 27% of patients were frail and 72% non-frail (Manier et al., 2025). Among frail patients at the 60-month follow-up, Isa-VRd improved PFS by 48.2% and increased MRD negativity rates (47.8% vs. 22.0%) compared with VRd, with overall survival rates of 48.8% vs. 43.7%, respectively (Cortese, 2025).

The CEPHEUS trial demonstrated consistent benefit for D-VRd over VRd alone, with a 54-month PFS of 68.1% vs. 49.5% (HR, 0.51; 95% CI = 0.35–0.74; $p = .0003$; Usmani et al., 2025). Daratumumab-VRd also produced higher rates of MRD negativity (54.4% vs. 29.3%) and sustained MRD negativity for ≥ 12 months (47.2% vs. 28.3%; Facon et al., 2025). At a median follow-up of nearly 59 months, PFS remained superior with D-VRd (69.0% vs. 48.0%; Facon et al., 2025). In a subgroup analysis using the IMWG frailty scale, 63.7% of patients who received D-VRd and were described as fit achieved MRD negativity compared with 44.7% with VRd. In intermediate-fit patients, 66.2% vs. 28.8% with VRd achieved MRD negativity (Facon et al., 2025). Given the exclusion of patients with poor performance status or age > 80, the true benefit for these individuals remains unknown (Table 2).

SAFETY

Discontinuation rates due to treatment-emergent adverse events (TEAEs) in the IMROZ trial were comparable, with 22.8% of Isa-VRd patients vs. 26.0% for VRd, possibly reflecting improved disease control mitigating toxicity. Notably, grade 3 to 4 pneumonia was most common in patients aged > 75 years receiving Isa-VRd (Cortese, 2025). In frail patients, TEAEs were nearly universal with both Isa-VRd and VRd (100% vs. 98%). Grade ≥ 3 TEAEs were also frequent (91.2% vs. 88%), and grade 5 events occurred more often with Isa-VRd (13.2% vs. 10%). Among non-frail patients, rates of any-grade TEAEs were similarly high (99.5% vs. 98.4%), but grade ≥ 3 events were more common with Isa-VRd (91.7% vs. 82%), as were grade 5 events (10.4% vs. 3.9%). In frail patients, the most common severe toxicity was neutropenia, occurring in 36.8% with Isa-VRd compared with 16% with VRd (Cortese, 2025).

The CEPHEUS regimen demonstrated a safety profile consistent with prior quadruplet studies. Hematologic toxicities, particularly neutropenia and thrombocytopenia, were more frequent with

Table 1. Key Eligibility Criteria and Study Design Features of the CEPHEUS and IMROZ Trials

	CEPHEUS trial	IMROZ trial
Study phase and design	Phase III, randomized, open-label	Phase III, randomized, open-label
Treatment arms	D-VRd (daratumumab, bortezomib, lenalidomide, dexamethasone) vs. VRd	Isa-VRd (isatuximab, bortezomib, lenalidomide, dexamethasone) vs. VRd
Frailty assessment	Prospective assessment using the original IMWG frailty score[a]	Retrospective assessment using the simplified IMWG frailty score
Performance status	ECOG 0–2	ECOG 0–2
Key inclusion criteria	IMWG-defined newly diagnosed multiple myeloma; adequate organ function; transplant-ineligible or transplant-deferred	IMWG-defined newly diagnosed multiple myeloma; adequate organ function; transplant-ineligible or transplant-deferred
Primary endpoint	Minimal residual disease negativity at 10^{-5} by next-generation sequencing	Progression-free survival

Note. D-VRd = daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG = Eastern Cooperative Oncology Group; IMWG = International Myeloma Working Group; Isa-VRd = isatuximab, bortezomib, lenalidomide, and dexamethasone; MRD = minimal residual disease; VRd = bortezomib, lenalidomide, and dexamethasone. Information from Usmani et al. (2025); Facon et al. (2024); Manier et al. (2025).
[a]Frailty assessment methodology differed between trials.

D-VRd, whereas rates of peripheral neuropathy were similar between treatment arms. Exposure-adjusted grade 5 events were comparable, and despite higher rates of serious TEAEs, D-VRd was associated with lower treatment discontinuation due to adverse events (Manier et al., 2025).

DISCUSSION

The treatment paradigm for newly diagnosed transplant-ineligible multiple myeloma (NDTIMM) has evolved substantially over the past two decades, driven by the introduction of proteasome inhibitors, immunomodulatory drugs, and CD38-directed monoclonal antibodies. In 2005, standard therapy for MM typically consisted of a novel agent combined with dexamethasone, regardless of transplant eligibility. In contrast, current frontline standards of care for both transplant-eligible and transplant-ineligible patients commonly incorporate CD38-based quadruplet regimens. The IMROZ and CEPHEUS trials demonstrated improved outcomes with quadruplet therapy compared with triplet regimens, including among patients categorized as frail or intermediate-fit (Usmani et al., 2025; Manier et al., 2025).

These advances have translated into marked improvements in depth of response and survival. However, these gains have been accompanied by increasing treatment intensity, progressing from doublet to triplet and now quadruplet regimens. While intensification has improved outcomes across broad patient populations, its application in frail and medically complex patients remains challenging. Older adults represent a growing proportion of patients with NDTIMM. Frailty, comorbidities, and organ dysfunction frequently limit treatment tolerability and complicate decision-making.

In both studies, NDTIMM patients were randomized to receive either a CD38 monoclonal antibody, proteasome inhibitor, immunomodulatory drug, and corticosteroid (quadruplet) or a triplet lacking the CD38 antibody. Patients were further stratified by frailty status to assess safety and efficacy (Usmani et al., 2025; Manier et al., 2025). Subgroup analyses revealed that frail patients experienced lower PFS, reduced MRD negativity rates, and higher toxicity compared with non-frail patients. Nonetheless, the quadruplet regimen provided superior PFS and MRD outcomes compared with triplet therapy in this population (Manier et al., 2025).

Multiple frailty scoring systems exist, but no standardized tool is universally accepted, which complicates cross-trial comparisons and clinical decision-making. The following discussion explores outcomes for frail MM patients treated with quadruplet regimens and highlights opportunities to improve evidence generation in this understudied subgroup.

Table 2. Outcomes of Quadruplet Therapy in Frail or Intermediate-Fit Patients With Newly Diagnosed Multiple Myeloma

Outcome category	Trial	Frailty group	Quadruplet regimen (Isa-VRd or D-VRd)	Triplet comparator (VRd)	Observed benefit in frail/intermediate-fit patients
MRD negativity (any timepoint)	IMROZ	Frail (sIMWG-defined)	47.8%	22.0%	Quadruplet more than doubled MRD negativity in frail patients
Sustained MRD negativity (12 months)	IMROZ	Overall; frail not separately reported	47%	24%	Sustained MRD significantly higher with quadruplet; magnitude likely maintained in frail subgroup
MRD negativity (intermediate-fit)	CEPHEUS	Intermediate-fit (no formal frail patients enrolled)	54.4%	29.3%	MRD negativity nearly doubled with quadruplet therapy
ORR	IMROZ	Frail	Higher ORR across all frailty levels (frail-specific ORR not published)	Lower ORR	Improvement in response across frailty categories; frail patients still benefited
PFS improvement	IMROZ	Frail	48.2% PFS improvement vs VRd	–	Quadruplet reduced risk of progression in frail patients by nearly half
PFS (60-month landmark)	IMROZ	Overall (frail not separately published at 60 mo)	63.2%	45.2%	Absolute 18% PFS improvement; frail subgroup analyses directionally similar
PFS (54-month landmark)	CEPHEUS	Intermediate-fit	68.1%	49.5%	~19% absolute benefit for intermediate-fit patients

Note. D-VRd = daratumumab, bortezomib, lenalidomide, and dexamethasone; IMWG = International Myeloma Working Group; Isa-VRd = isatuximab, bortezomib, lenalidomide, and dexamethasone; MRD = minimal residual disease; NDMM = newly diagnosed multiple myeloma; ORR = overall response rate; PFS = progression-free survival; sIMWG = simplified IMWG frailty score; VRd = bortezomib, lenalidomide, and dexamethasone. Information from Usmani et al. (2025); Manier et al. (2025); Facon et al. (2024, 2025).

In IMROZ, Isa-VRd significantly improved PFS and MRD outcomes compared with VRd alone. Among frail patients, Isa-VRd nearly doubled MRD negativity rates and improved PFS relative to triplet therapy, although absolute outcomes remained inferior to those observed in non-frail patients. Similarly, CEPHEUS demonstrated consistent benefit with D-VRd, including higher rates of sustained MRD negativity across frailty strata. These findings support the NCCN's designation of quadruplet therapy as a Category 1–preferred option for transplant-ineligible patients (NCCN, 2025).

Despite these gains, toxicity remains a critical concern. In both IMROZ and CEPHEUS, treatment-emergent adverse events were nearly universal, particularly among frail patients. Rates of grade ≥ 3 toxicities exceeded 90% across treatment arms, with hematologic adverse events (most notably neutropenia) occurring more frequently with quadruplet therapy. Grade 5 events were also more common in frail patients receiving Isa-VRd compared with VRd alone. Although treatment discontinuation rates were comparable or lower with quadruplet therapy, these toxicity patterns underscore the narrow therapeutic window in frail populations.

The applicability of trial results to real-world practice is further limited by restrictive eligibility criteria. Patients older than 80 years, those with poor performance status, and individuals with significant comorbidities were excluded from both trials, despite representing a substantial proportion of real-world patients. Additionally, both studies employed twice-weekly bortezomib during induction, a schedule associated with higher rates of peripheral neuropathy and

treatment discontinuation than the once-weekly dosing commonly used in practice (Hoff et al., 2024). Similarly, dexamethasone dosing was not routinely adjusted for advanced age or frailty, despite IMWG guideline recommendations supporting lower starting doses in older adults.

Real-world data suggest that adoption of intensive frontline regimens remains incomplete, even following regulatory approval. This likely reflects clinician concern regarding tolerability, particularly in vulnerable patients. To optimize outcomes, treatment strategies for frail patients should prioritize individualized dose and schedule modifications, including weekly bortezomib, age-adjusted dexamethasone, and careful renal-based lenalidomide dosing. Importantly, future clinical trials must deliberately include patients traditionally considered "too frail" to generate evidence that better reflects routine clinical practice.

In summary, frontline quadruplet therapy improves efficacy outcomes in NDTIMM, including in those patients categorized as frail. However, toxicity remains substantial, and trial populations do not fully represent the most vulnerable patients encountered in practice. Balancing treatment intensity with tolerability through thoughtful regimen modification and more inclusive research designs is essential to advancing care for this growing patient population.

REAL-WORLD IMPLICATIONS

Although quadruplet regimens were not FDA approved until September 2024, limited off-trial adoption was observed. Real-world Flatiron Health electronic medical record data (2016–2023) showed frontline use of VRd (52.3%), lenalidomide–dexamethasone (17.4%), and daratumumab–VRd (10.0%) in newly diagnosed, transplant-eligible patients (Lin et al., 2024). While this analysis excluded frail individuals, it highlights ongoing underutilization of intensive therapy despite growing evidence of benefit.

To meaningfully improve outcomes for frail MM patients, future trials must prioritize inclusivity by enrolling patients often deemed "too frail." Only by capturing real-world toxicity and efficacy data in these individuals can clinicians develop more precise, evidence-based strategies balancing treatment intensity with patient resilience. In the interim, to achieve the best outcomes for frail patients, as clinicians we must consider strategies that could potentially mitigate toxicity exposure with more intensive therapy. In both trials, patients in each treatment arm received twice-weekly bortezomib—an approach associated with higher rates of grade 3 to 4 neuropathy and increased treatment discontinuation compared with the once-weekly dosing schedule commonly used in clinical practice (Hoff et al., 2024). Furthermore, both trials did not specify age-adjusted dexamethasone dosing for elderly patients with the standard dose of 40 mg weekly regardless of age. The American Society of Clinical Oncology (ASCO) recommends a starting dose of 20 mg weekly for patients older than 75 years and a body mass index less than 18.5 (Mikhael et al., 2019). Doses can be further reduced to as low as 8 mg once weekly for frail patients and those with poor tolerability. The recommendation is based on the increased incidence of infection, diabetes, fluid retention, and hypertension in this population (Mikhael et al., 2019). In addition, renal impairment is frequently found in the elderly and poses a risk for lenalidomide toxicity. It is important that renal function is closely monitored in these patients and that proper dose adjustments are made (Mikhael et al., 2019).

CLINICAL TAKEAWAYS FOR ADVANCED PRACTICE PROVIDERS

Quadruplet regimens incorporating a CD38 monoclonal antibody with bortezomib, lenalidomide, and dexamethasone have emerged as a preferred frontline treatment strategy for patients with NDTIMM, demonstrating improved depth of response, higher MRD-negativity rates, and longer PFS compared with traditional triplet therapy. These benefits have been observed even in patients with intermediate fitness or frailty when carefully selected. However, the increased treatment intensity associated with quadruplet therapy requires thoughtful clinical application in older adults and medically complex patients.

Advanced practice providers play a critical role in optimizing outcomes by incorporating formal frailty assessments, closely monitoring for treatment-emergent toxicities, and implementing proactive supportive care strategies. Dose and schedule modifications, such as once-weekly

bortezomib administration, age-adjusted dexamethasone dosing, and renal-adjusted lenalidomide dosing, may improve tolerability while maintaining therapeutic benefit. Given that many pivotal trials exclude the oldest and most frail patients, real-world clinical judgment remains essential when individualizing therapy. Ultimately, balancing treatment intensity with patient resilience, comorbidities, and functional status is central to maximizing disease control while minimizing toxicity in this growing population of transplant-ineligible MM patients.

CONCLUSION

Over the past several decades, treatment advancements in MM have significantly improved patient outcomes. However, these benefits have not been uniformly realized; frail patients continue to experience disproportionately poorer outcomes. Real-world data reveal a trend toward deescalation of therapy within this vulnerable group, often driven by toxicity concerns and limited evidence to guide optimal management.

To address this gap, clinical research must prioritize the standardization of frailty assessment and its prospective integration into trial design. Interpretation of currently available data is complicated not only by the absence of a universally accepted frailty model, but also by important differences in study populations across key frontline trials. IMROZ enrolled a strictly transplant-ineligible population, making its results more directly applicable to patients who are not candidates for ASCT. In contrast, CEPHEUS included a broader frontline population that included patients who had deferred ASCT rather than being definitively transplant ineligible, introducing a fitter subgroup that may have influenced efficacy and tolerability outcomes. This distinction is important because patients who defer transplant may differ substantially from patients who are biologically frail, older, or medically ineligible for transplant, and therefore may not accurately reflect the vulnerability seen in routine transplant-ineligible practice.

The concept of "frailty" itself also warrants closer examination. Frailty is not synonymous with age, transplant ineligibility, or ECOG performance status alone. Rather, it reflects a multidimensional state incorporating comorbidity burden, functional capacity, cognition, mobility, and physiologic reserve. In CEPHEUS, frailty was assessed using the original IMWG frailty score, which incorporates age, Charlson Comorbidity Index, Activities of Daily Living, and Instrumental Activities of Daily Living, whereas IMROZ used the simplified IMWG frailty score, which substitutes ECOG performance status for functional measures. Although both approaches attempt to stratify patient vulnerability, they are not interchangeable. A patient categorized as frail by one model may not be classified the same way by another, limiting cross-trial comparison and creating uncertainty when translating subgroup findings into real-world practice. Moreover, the frail patients enrolled in clinical trials are often still highly selected, as both studies excluded many individuals seen commonly in practice, including patients older than 80 years, those with marked organ dysfunction, significant neuropathy, or poor performance status. As a result, trial-defined frailty may underrepresent the degree of vulnerability encountered in community oncology clinics.

Future studies should therefore move beyond broad frailty labels and more clearly characterize the spectrum of vulnerability within transplant-ineligible MM. Expanding inclusion criteria, harmonizing frailty definitions, and developing dedicated prospective registries for elderly, comorbid, and functionally impaired patients would generate more clinically relevant evidence to guide individualized treatment strategies. Such efforts are essential to determine which patients can benefit from treatment intensification, which require modified regimens, and how best to balance efficacy with tolerability so that progress in frontline myeloma therapy is more equitable across all patient subgroups. ●

Disclosure

The author has served on speaker bureaus for GlaxoSmithKline, Janssen Pharmaceuticals (Johnson & Johnson), Geron Corporation, and Incyte Corporation.

References

Cortese, T. (2025). Isa-VRd shows efficacy and safety in frail transplant-ineligible myeloma. *Cancer Network*. https://

www.cancernetwork.com/view/isa-vrd-shows-efficacy-and-safety-in-frail-transplant-ineligible-myeloma

Facon, T., Dimopoulos, M. A., Leleu, X. P., Beksac, M., Pour, L., Hajek, R., Liu, Z., Minarik, J., Moreau, P., Romejko-Jarosinska, J., Spicka, I., Vorobyev, V. I., Cavo, M., Goldschmidt, H., Martin, T. G., Manier, S., Brégeault, M.-F., Macé, S., Berthou, C., & Orlowski, R. Z. (2024). Phase 3 study results of isatuximab, bortezomib, lenalidomide, and dexamethasone (Isa-VRd) versus VRd for transplant-ineligible patients with newly diagnosed multiple myeloma (IMROZ). *Journal of Clinical Oncology, 42*(16_suppl), 7500. https://doi.org/10.1200/JCO.2024.42.16_suppl.7500

Facon, T., Zweegman, S., Hungria, V., Bahlis, N. J., Venner, C., Braunstein, M., Pour, L., Marti Tutusaus, J. M., basu, s., Cohen, Y., Matsumoto, M., Suzuki, K., Hulin, C., Grosicki, S., Beksac, M., Maiolino, A., Wang, J., van Brummelen, E., Lopez-Masi, L., Carey, J., Rowe, M., Carson, R., & Usmani, S. Z. (2025). Daratumumab plus bortezomib, lenalidomide, and dexamethasone in patients with newly diagnosed multiple myeloma: Subgroup analysis of transplant-ineligible patients in the phase 3 CEPHEUS study (Abstract PS1730). EHA Library. https://library.ehaweb.org/eha/2025/eha2025-congress/4160805/thierry.facon.daratumumab.plus.bortezomib.lenalidomide.and.dexamethasone.in.html?f=

Hoff, F. W., Banerjee, R., Khan, A. M., McCaughan, G., Wang, B., Wang, X., Roose, J., Anderson, L. D., Jr, Cowan, A. J., Rajkumar, S. V., & Kaur, G. (2024). Once-weekly versus twice-weekly bortezomib in newly diagnosed multiple myeloma: a real-world analysis. *Blood Cancer Journal*, *14*(1), 52. https://doi.org/10.1038/s41408-024-01034-6

Kaplan, D. A. (2022). Multiple myeloma: Top 10 advances in the past 10 years. *Targeted Therapies in Oncology, 11*(4), 70.

Lin, F., Gallienne, S., Ionescu-Ittu, R., Sasane, M., Minasyan, A., Tekle, C., & Richter, J. (2024). Understanding frontline therapy pattern, attrition rates and survival outcomes in patients with newly diagnosed multiple myeloma who underwent transplant. *Blood, 144*(Suppl 1), 3761. https://doi.org/10.1182/blood-2024-201296

Manier, S., Dimopoulos, M. A., Leleu, X. P., Moreau, P., Cavo, M., Goldschmidt, H., Orlowski, R. Z., Tron, M., Tekle, C., Brégeault, M. F., Shafer, A. T., Beksac, M., & Facon, T. (2025). Isatuximab plus bortezomib, lenalidomide, and dexamethasone for transplant-ineligible newly diagnosed multiple myeloma patients: A frailty subgroup analysis of the IMROZ trial. *Haematologica*, *110*(9), 2139–2150. https://doi.org/10.3324/haematol.2024.287200

Mikhael, J., Ismaila, N., Cheung, M. C., Costello, C., Dhodapkar, M. V., Kumar, S., Lacy, M., Lipe, B., Little, R. F., Nikonova, A., Omel, J., Peswani, N., Prica, A., Raje, N., Seth, R., Vesole, D. H., Walker, I., Whitley, A., Wildes, T. M., Wong, S. W.,...Martin, T. (2019). Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. *Journal of Clinical Oncology*, *37*(14), 1228–1263. https://doi.org/10.1200/JCO.18.02096

Moore, K. L. F., Turesson, I., Genell, A., Klausen, T. W., Knut-Bojanowska, D., Redder, L., Sverrisdottir, I., Thorsen, J., Vangsted, A. J., & Blimark, C. H. (2023). Improved survival in myeloma patients-a nationwide registry study of 4,647 patients ≥75 years treated in Denmark and Sweden. *Haematologica*, *108*(6), 1640–1651. https://doi.org/10.3324/haematol.2021.280424

National Comprehensive Cancer Network. (2025). *NCCN clinical practice guidelines in oncology: Multiple myeloma (Version 3.2025)*. https://www.nccn.org

Usmani, S. Z., Facon, T., Hungria, V., Bahlis, N. J., Venner, C. P., Braunstein, M., Pour, L., Martí, J. M., Basu, S., Cohen, Y. C., Matsumoto, M., Suzuki, K., Hulin, C., Grosicki, S., Legiec, W., Beksac, M., Maiolino, A., Takamatsu, H., Perrot, A., Turgut, M.,...Zweegman, S. (2025). Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: The randomized phase 3 CEPHEUS trial. *Nature Medicine*, *31*(4), 1195–1202. https://doi.org/10.1038/s41591-024-03485-7