

CLINICAL PRACTICE GUIDELINE

Treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation

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Introduction

The treatment paradigm for multiple myeloma (MM) has evolved considerably. The development of novel therapies has resulted in significant improvement in the progression free survival (PFS) and overall survival (OS) of patients.¹ A fundamental initial step in the management of newly diagnosed MM (NDMM) is distinguishing between patients who are fit for induction followed by consolidative high-dose therapy and autologous stem cell transplantation (HDT + ASCT), versus those who are transplant ineligible (TIE).

TIE patients are usually older (typically aged >70 years) and/or have been assessed to be at a higher risk of treatment-related toxicities, secondary to comorbidities and frailty, where less toxic regimens are more suitable.

TIE patients are a highly heterogeneous population. Accordingly, a comprehensive frailty assessment represents an integral part of the initial assessment to enable an individualised, frailty-adapted treatment approach.^{2,3}

With modern therapies, deep and/or durable responses are now achievable in TIE patients.^{4,5}

These guidelines have been developed by the Medical and Scientific Advisory Group (MSAG) to Myeloma Australia to provide clinicians with an up-to-date, evidence-based, and practical framework for the management of TIE patients with newly diagnosed MM in the Australian context.

Levels of evidence and grades of recommendations used in these guidelines are listed in Table 1.

Table One

Levels of evidence and grades of recommendations

LEVELS OF EVIDENCE	
1A	Evidence from meta-analysis of randomised controlled trials.
1B	Evidence from at least one randomised controlled trial.
2A	Evidence from at least one well-designed non-randomised trial, including Phase II trials and case-control studies.
2B	Evidence from at least one other type of well-designed, quasi-experimental study such as observational studies.
3	Evidence from well-designed non-experimental descriptive studies.
4	Evidence obtained from expert committee reports or opinions and/or of respected authorities.
GRADES OF RECOMMENDATIONS	
A	Recommendation based on at least one randomised controlled trial of good quality addressing specific recommendation (Evidence level 1A and 1B).
B	Recommendation based on well-conducted studies but no randomised controlled trial on topic of recommendation (Evidence level 2A, 2B, and 3).
C	Recommendation based on expert opinions or reports (Evidence level 4).

Pre-treatment considerations: Frailty assessment

A cut off age of 65 years old for transplant eligibility is no longer considered appropriate. **Figure 1** summarises the treatment decision algorithm for patients with NDMM.

There is increasing recognition that TIE patients are at risk of being under- or over-treated. Given the heterogeneity within the population of TIE patients, the balance of treatment effectiveness and toxicity is challenging to achieve and requires a nuanced approach. Upfront stratification of patients across the fitness spectrum allows for an individualised treatment strategy and better outcomes. There are several frailty assessment frameworks, including the International Myeloma Working Group Frailty Index (IMWG-FI)⁶, simplified frailty scale⁷ and the Mayo Frailty Index⁸. **Table 2** provides a summary of these frailty assessment tools (please also refer to the MSAG position paper on the importance of frailty assessment²). We recommend using the IMWG-FI instrument, which stratifies patients into three categories (fit, intermediate-fit and frail). It is an independent predictor of adverse events, early drug discontinuation and OS, irrespective of staging and treatment regimen.⁶ Fit patients should receive treatment that prioritises efficacy, while intermediate-fit patients and frail patients should receive dose-attenuated treatment that balances efficacy and toxicity.

Induction treatment

Triplet/quadruplet versus doublet therapy and the role of anti-CD38 monoclonal antibodies

According to real-world data from the Australian Myeloma and Related Disease Registry, attrition rates increase with each successive line of treatment (<https://mrd.net.au>) and relatively few patients are exposed to a third-line treatment. This underscores the need to use the most optimal treatment regimens early in the disease course.

In TIE patients, more intensive treatment with complex multi-drug regimens is not necessarily beneficial. **Table 3** summarises commonly used induction regimens for these patients. Upfront dose attenuation should be considered, particularly in the intermediate-fit and frail patients (**Table 4**).^{2, 3} Where accessible, clinical trials that allow for frailty-adjusted, or response-adapted, therapy should be considered.

Triplet therapies and the role of anti-CD38 monoclonal antibodies

The anti-CD38 monoclonal antibody (mAb), daratumumab is effective in relapsed myeloma^{9,10}, and has been applied in the front-line setting. This was demonstrated in the MAIA study⁵, where combination daratumumab with Rd (Dara-Rd) was associated with longer PFS (61.9m vs 34.4m; HR 0.55 p<0.0001), tripling of minimal residual disease (MRD) negativity rates and longer OS (not reached vs. 65.5m; HR 0.66, p=0.0003), when compared to Rd. In a frailty subgroup analysis, nearly 50% of patients in the MAIA study were confirmed as frail as per IMWG-FI, with a sustained PFS benefit in this subpopulation.¹¹

Triplet therapy with Dara-Rd is internationally regarded as the standard-of-care induction in TIE patients. As of March 2025, this combination has received positive recommendation by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) for funding and has been listed on the Pharmaceutical Benefits Scheme (PBS).

Other triplet combinations available for the treatment of TIE patients include VRd-lite (bortezomib-lenalidomide-dexamethasone) and VCD (bortezomib-cyclophosphamide-dexamethasone). VRd was PBS-reimbursed in June 2020 for the treatment of NDMM based on the SWOG S0777 study. This Phase III study compared VRd to Rd in patients who were not planned for upfront ASCT.¹² Bortezomib was administered intravenously on a twice-weekly schedule (1.3mg/m² Days 1,4,8,11; 21-day cycle). At a median follow up of 84 months, median PFS and OS were superior in the VRd cohort (PFS 41m vs. 29m, HR 0.742, p=0.003; OS NR vs. 69m, HR 0.709, p=0.0114). However, it is important to note that only 43% of patients in this study were >65 years of age, and a significant proportion of patients were not truly TIE, with 68% of patients intended for transplant. Rates of peripheral neuropathy (PN) were significant with intravenous, twice-weekly bortezomib dosing; all grade PN occurred in 80% of patients with ≥Grade 3 PN reported in 33% of patients. By extrapolating these data, it would be expected that even higher rates of PN would be observed in patients who are truly TIE.

Due to significant toxicities with twice-weekly bortezomib, and evidence demonstrating equivalent efficacy with weekly dosing^{13,14}, many clinicians use a “VRd-lite” regimen in TIE patients who are fit according to IMWG-criteria.

A small Phase II study (n=50) by O’Donnell et al.¹⁵ demonstrated that a “VRd-lite” regimen, with weekly subcutaneous bortezomib (1.3mg/m² Days 1,8,15,22; 35-day cycle), had comparable efficacy but with lower toxicity rates in TIE patients (median age 73 years (65–92)). Only one patient in this study had ≥Grade 3 PN. As such, MSAG recommends a subcutaneous weekly bortezomib regimen to minimise toxicity risk. Further upfront dose attenuation can also be considered for individual patients (**Table 4**). It is however important to note that triplet “VRd-lite” has not been directly compared to Rd.

The addition of an alkylating agent to Rd is not recommended. Post-hoc analysis of the EMN01 trial according to IMWG-FI frailty scoring concluded that melphalan-prednisolone-lenalidomide and lenalidomide-cyclophosphamide-dexamethasone induction had no PFS or OS advantage when compared to Rd in intermediate-fit and frail patients.¹⁶

Anti-CD38 monoclonal antibody-based quadruplet therapy

With the success of the MAIA study, and in an effort to improve on current standard-of-care, three Phase III studies have investigated the benefits of anti-CD38 mAb-based quadruplet therapy with daratumumab or isatuximab (Isa) in combination with VRd in NDMM TIE patients. The IMROZ study compared Isa-VRd followed by Isa-Rd versus VRd followed by Rd (twice-weekly bortezomib regimen) and showed that addition of Isa resulted in a significant improvement in estimated PFS at 60 months of 63.2% versus 45.2% in the VRd group.¹⁷ The results of this study are supported by the CEPHEUS study which randomised TIE or transplant deferred patients to Dara-VRd or VRd (twice-weekly bortezomib regimen) followed by Dara-Rd or Rd until progression.¹⁸ This study demonstrated the addition of daratumumab improved MRD negativity rates at 10^{-5} at 60.9% vs 39.4%. Finally, the BENEFIT study explored the role of bortezomib in quadruplet therapy in TIE patients by randomising patients to Isa-VRd (weekly bortezomib) or Isa-Rd. The addition of bortezomib significantly improved the primary endpoint of MRD negativity; at 18 months after randomisation, MRD-negativity was 53% vs 26% (odds ratio 3.16, $p < 0.0001$) respectively.¹⁹ No survival benefit has been reported at a median follow-up of 23.5 months.

While investigators have recommended that quadruplet Dara-VRd or Isa-VRd should be the new standard-of-care in NDMM TIE patients, it is important to note that all three studies excluded patients aged ≥ 80 yo. In a post-hoc analysis of IMROZ, patients were stratified as per the simplified frailty score; majority (72%) of patients in this study were non-frail.²⁰ While benefits of Isa-VRd were still seen in the frail cohort, it does raise the applicability of a quadruplet therapy to the truly frail elderly population.

Doublet therapies

In older frail patients, prioritising treatment tolerance allows for longer time on treatment and improved patient outcomes. Weighing the risks against benefits, such patients often benefit from doublet over triplet therapy, with the exception of Dara-Rd which is highly tolerable even in the frail population.¹¹

Acknowledging the limitations of cross-comparison across trials, median PFS reported by O'Donnell et al.¹⁵ for VRd-lite was similar to that of patients in the Rd arm of the MAIA study^{5, 21} (35.1m and 34.4m respectively). Furthermore, in the MAIA subgroup analysis by frailty status, median PFS in the "fit" and "intermediate-fit" patients was 41.7 months in the Rd group¹¹. Indeed, Rd is an acceptable treatment in TIE patients. Ongoing Rd treatment is important; the FIRST study analysed the outcomes of NDMM TIE patients who were treated with Rd until disease progression (Rd-continuous) versus Rd for 18 cycles (Rd18) versus MPT (melphalan-prednisolone-thalidomide).⁴ With appropriate dose modifications, Rd-continuous allowed for response maintenance and improved PFS compared to the MPT cohort, with more than doubling of the 4-year PFS rates (32.6% vs 13.6%, HR 0.69; $p < 0.0001$). Outcomes were independent of the depth of response.

For patients with significant renal impairment, weekly Vd is an alternative option. In the evaluation of bortezomib-based doublet and triplet therapies, Vd has been demonstrated to be better tolerated with fewer discontinuations compared to bortezomib-melphalan-prednisolone and bortezomib-thalidomide-dexamethasone, with equivalent efficacy in frailer patients.²²

Recommendations for pre-treatment considerations and induction therapies in TIE patients

→ In all patients, consideration should be given to enrolment into a clinical study if one is available.

→ All patients considered TIE should have a frailty assessment at diagnosis. MSAG recommends the IMWG-FI as the instrument of choice for frailty stratification.

→ TIE patients who are IMWG-FI “fit” should receive induction with an anti-CD38 mAb-based triplet therapy, with the aim of achieving deep remission (Grade A recommendation, Level 1A evidence). There is now evidence supporting the use of anti-CD38 mAb-based quadruplet therapy in this population, although this is not currently accessible via the PBS in Australia.

→ IMWG-FI “intermediate-fit” and “frail” patients should receive anti-CD38 mAb-based triplet therapy, or doublet therapy (incorporating an IMiD or PI), with appropriate dose attenuation and priority given to toxicity minimisation.

→ Upfront dose attenuation should be considered based on frailty stratification (**Table 4**).

→ Combination Dara-Rd is a highly effective and well tolerated triplet regimen, even in IMWG-FI “frail” patients, and is considered standard-of-care for all TIE patients (Grade A recommendation, Level 1A evidence).

→ Other triplet therapy options include:

→ “VRd-lite” with weekly subcutaneous bortezomib is recommended to optimise deliverability and minimise the risk of early treatment cessation secondary to treatment-related adverse events, in particular peripheral neuropathy. (Grade B recommendation, Level 2A evidence)

→ VCD (utilizing weekly subcutaneous bortezomib)

→ Options for doublet therapy include:

→ Rd (with aim to cease dexamethasone after 9 cycles). (Grade A recommendation, Level 1A evidence)

→ In patients with renal impairment, Vd could be considered. (Grade B recommendation, Level 1B evidence)

→ To minimise peripheral neuropathy:

→ Subcutaneous route of bortezomib administration is preferred to intravenous route.

→ Weekly bortezomib is recommended over twice-weekly regimen.

→ Adequate supportive care is vital and all patients should receive a multidisciplinary model of care, with consideration of early involvement of the palliative care team for symptom management where appropriate.

Maintenance Therapy

The benefits of lenalidomide maintenance therapy in TIE patients have been clearly demonstrated in pivotal Phase III trials. The landmark analysis of the MM015 study²³, which compared fixed duration MP (melphalan-prednisolone) versus fixed duration MPR (melphalan-prednisolone-lenalidomide) versus MPR with lenalidomide maintenance (MPR-R), demonstrated that the use of maintenance therapy reduced the rate of progression amongst all patients, irrespective of age, by 66% when compared to placebo. Results showed a median PFS advantage of 18 months (MPR-R vs MP). The clinical benefit of this is significant, considering a proportion of older TIE patients may not tolerate second line therapy. In the final analysis of the FIRST study, Rd-continuous had a ~30-month longer median time-to-next-treatment when compared to Rd18 in patients who achieved complete or very good partial responses (69.5 vs 39.9m).⁴ The Rd-R study by Larocca et al. demonstrated that planned cessation of dexamethasone with continuation of low-dose lenalidomide (10mg, days 1 to 21 every 28 days) as maintenance after 9 cycles of Rd resulted in equivalent outcomes when compared to Rd-continuous, but with superior event-free survival in intermediate-fit patients.²⁴

The benefit of maintenance therapy in prolonging PFS has also been seen with proteasome inhibitors, including ixazomib.²⁵ Phase III studies on TIE patients have also incorporated bortezomib maintenance with positive results, although noting these trials were not designed to assess the isolated effect of bortezomib maintenance.^{26, 27} Currently, these drugs are not PBS-reimbursed for maintenance therapy.

While the benefits of maintenance treatment are evident, maintenance should never be administered at expense of toxicity, particularly in a cohort of patients with lower physiological reserve.

BOX TWO

Recommendations for maintenance therapies in TIE patients

- For patients who have a lenalidomide-based induction, lenalidomide monotherapy is a tolerable and effective maintenance therapy, with prolongation of PFS. (Grade A recommendation, Level 1A evidence)
- The benefit of bortezomib maintenance therapy is unclear. (Grade A recommendation, Level 1B evidence)
- Ixazomib maintenance therapy (irrespective of induction regimen) has been shown to positively impact on PFS (but not OS). (Grade A recommendation, Level 1B evidence). Ixazomib is currently not PBS-reimbursed in Australia.
- While the benefits of maintenance treatment is evident, maintenance should never be administered at the expense of toxicity and quality-of-life.

Supportive Care

In TIE patients, early involvement of the allied health multidisciplinary team and adequate supportive care is vital. Early involvement of the palliative care team is also recommended for symptom management where appropriate. Please refer to Myeloma Australia's supportive care guidelines.

Conclusion

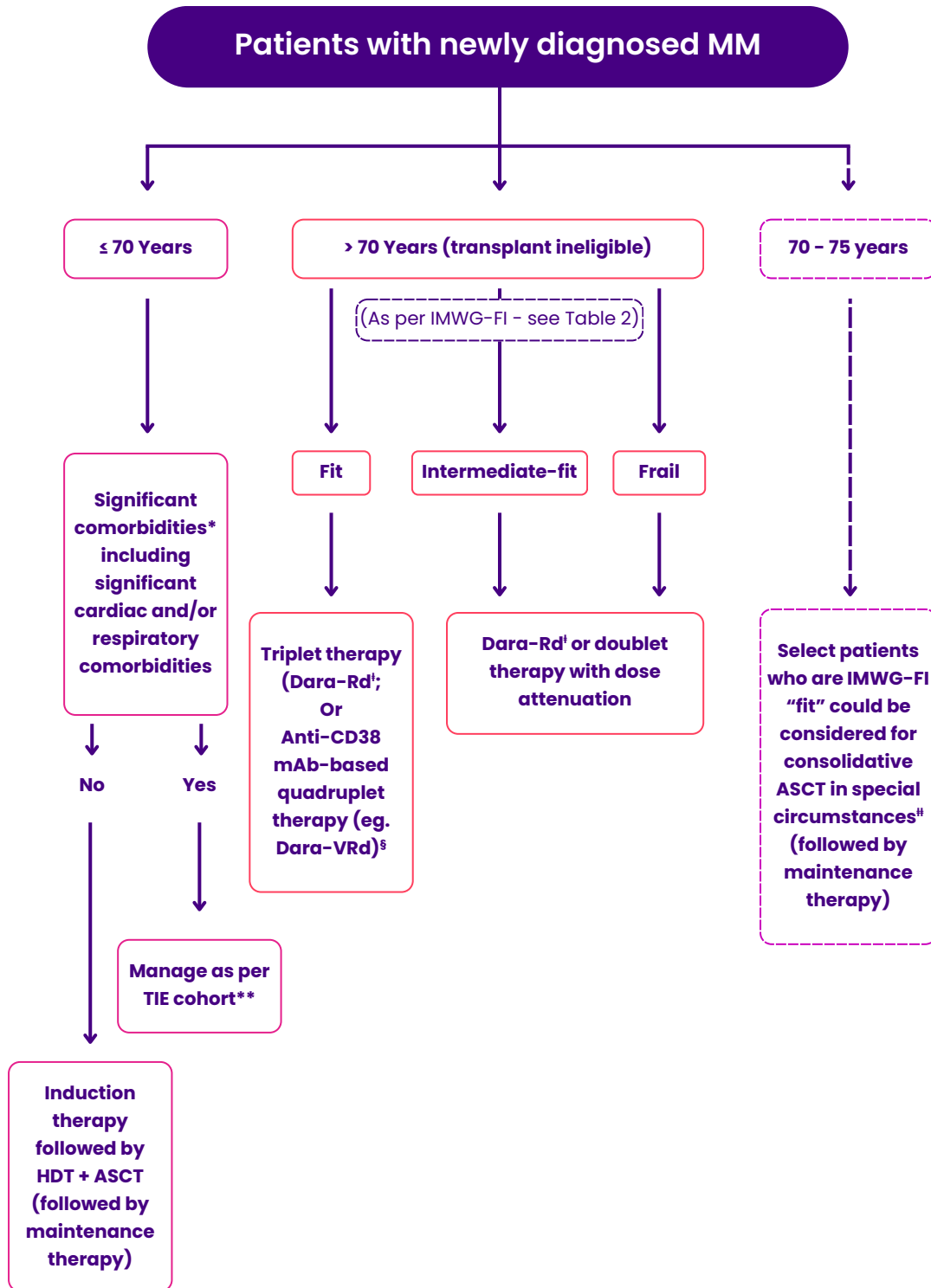
While more effective treatments have resulted in improved survival in the TIE population, treatment tolerability and deliverability remain the main challenge in clinical practice and are key factors that dictate patient outcomes. TIE patients should be stratified into IMWG-FI fit, intermediate-fit and frail to allow for a frailty-adapted treatment approach. With this consensus guideline, we aim to provide a best practice treatment algorithm for clinicians and hence improve care and treatment outcomes of TIE NDMM patients.

The above guideline is based on up-to-date information as of January 2026. Some aspect of this guideline may change in the future depending on emerging data from clinical studies. This guideline is due for review after January 2028.

The authors of this guideline declare no potential conflict of interest. This guideline was unsolicited and was established by members of the MSAG without the assistance of or influence by any other organisational body or pharmaceutical company.

Figure One

Treatment decision algorithm for induction treatment patients with NDMM



MM: Multiple myeloma; HDT + ASCT: High-dose melphalan and autologous stem cell transplantation. IMWG-FI: International Myeloma Working Group Frailty Index; Dara-Rd: Daratumumab, lenalidomide, dexamethasone; mAb: Monoclonal antibody; TIE: transplant ineligible; VRd: Bortezomib, lenalidomide, dexamethasone; VCD: Bortezomib, cyclophosphamide, dexamethasone

*Note that renal impairment is not a contraindication for an ASCT

**Recommend considering 'rainy day' stem cell collection in patients ≤70 years who are deemed TIE, especially in patients ≤65 years old

† Dara-Rd should be the standard-of-care induction treatment in TIE patients

Special circumstances could include patients with high-risk disease who would most benefit from high dose chemotherapy

§ Not currently available on Australian PBS

Table Two

Summary of frailty assessment tools²

Frailty assessments	Components	Score	Total score	Stratification
IMWG-FI⁽⁶⁾	Age, years			
	≤75	0		
	76-80	1		
	> 80	2		
	ADL		0	Fit
	>4	0		
	≤ 4	1	1	Intermediate Fit
	IADL			
	> 5	0	≥ 2	Frail
	≤ 5	1		
	CCI			
	≤ 1	0		
	> 1	1		

Frailty assessments	Components	Score	Total score	Stratification
Mayo Frailty Index ⁽⁸⁾	Age, years		0	Stage I
	≥ 70	1		
	ECOG-PS		1	Stage II
	≥ 2	1		
	NT-proBNP		2	Stage III
	≥300ng/L	1		
			3	Stage IV
Frailty assessments	Components	Score	Total score	Stratification
Simplified frailty scale ⁽⁷⁾	Age, years			
	≤75	0		
	76-80	1		
	> 80	2		
	CCI		0-1	Non-frail
	≤1	0		
	> 1	1	≥ 2	Frail
	ECOG-PS			
	0	0		
	1	1		
	≥ 2	2		

IMWG-FI: International Myeloma Working Group Frailty Index; ADL: Katz Activity of Daily Living; IADL: Lawton Instrumental Activity of Daily Living; CCI: Charlson Comorbidity Index; ECOG-PS: Eastern Cooperative Oncology Group performance status; NT-proBNP: N-terminal fragment of the type-B natriuretic peptide.

Table Three

Induction regimens for patients ineligible for autologous stem cell transplant

Dara-Rd	<p>MAIA study⁵:</p> <p>28-day cycle</p> <p>Daratumumab 16mg/kg IV*</p> <ul style="list-style-type: none"> → Cycle 1 and 2: D1,8,15,22 → Cycle 3 to 6: D1,15 → Cycle 7 onwards: D1 <p>Lenalidomide: 25mg PO; D1-21 (of 28 day cycle)</p> <p>Dexamethasone: 40mg PO; D1,8,15,22 (20mg if >75yo)</p> <p>*Subcutaneous daratumumab 1800mg can be used as alternative to IV dosing, with the same frequency as above.</p>
Rd	<p>Larocca et al.²⁴:</p> <p>28-day cycle</p> <p>Cycles 1 to 9:</p> <ul style="list-style-type: none"> → Lenalidomide: 25mg PO; D1-21 (of 28 day cycle) → Dexamethasone: 20mg PO; D1,8,15,22 <p>Cycle 10 onwards: Lenalidomide maintenance: 10mg PO; D1-21 (of 28 day cycle)</p>
VRd-lite	<p>O'Donnell et al.¹⁵:</p> <p>Induction – 9 x 35-day cycles:</p> <p>Bortezomib: 1.3mg/m² subcut; D1,8,15,22</p> <p>Lenalidomide: 15mg PO; D1-21 (of 28 day cycle)</p> <p>Dexamethasone: 20mg PO</p> <ul style="list-style-type: none"> → On D1,2,8,9,15,16,22,23 for patients ≤75yo → On D1,8,15,22 for patients >75yo <p>Consolidation – 6 x 28-day cycles:</p> <p>Bortezomib: 1.3mg/m² subcut; D1,15</p> <p>Lenalidomide: 15mg PO; D1-21 (of 28 day cycle)</p>
VCD	<p>28-day cycle (for up to 8 cycles):</p> <ul style="list-style-type: none"> → Bortezomib: 1.3mg/m² subcut; D1,8,15,22 → Cyclophosphamide: 300mg/m² PO; D1,8,15,22 → Dexamethasone: 40mg PO; D1,8,15,22
Vd	<p>28-day cycle (for up to 8 cycles):</p> <ul style="list-style-type: none"> → Bortezomib: 1.3mg/m² subcut; D1,8,15,22 → Dexamethasone: 40mg PO; D1,8,15,22
Dara-VRd	<p>CEPHEUS¹⁸:</p> <p>Cycle 1 to 8; 21-day cycles:</p> <p>Daratumumab: 1800mg subcut</p> <ul style="list-style-type: none"> → Cycle 1 and 2: Weekly → Cycle 3 to 8: Every 3 weeks <p>Bortezomib: 1.3mg/m² subcut; D1,4,8,11</p> <p>Lenalidomide: 25mg PO; D1-14</p> <p>Dexamethasone: 20mg PO; D1,2,4,5,8,9,11,12 (D1,4,8,11 if >75yo or BMI<18.5kg/m²)</p> <p>Cycle 9 onwards (until disease progression or unacceptable toxicity); 28-day cycles:</p> <p>Daratumumab: 1800mg subcut; D1</p> <p>Lenalidomide: 25mg PO; D1-21</p> <p>Dexamethasone: 40mg PO; D1,8,15,22 (20mg weekly if >75yo or BMI<18.5kg/m²)</p>

Isa-VRd	<p>BENEFIT¹⁹:</p> <p>Cycle 1 to 12; 28-day cycles Isatuximab: 10mg/kg IV → Cycle 1: D1,8,15,22 → Cycle 2 to 12: D1,15 Bortezomib: 1.3mg/m² subcut; D1,8,15 Lenalidomide: 25mg PO; D1-21 Dexamethasone: 20mg PO; D1,8,15,22</p> <p>Cycle 13 to 18; 28-day cycles: Isatuximab: 10mg/kg IV; D1 Bortezomib: 1.3mg/m² subcut; D1,15 Lenalidomide: 25mg PO; D1-21</p> <p>Cycle 19 onwards (until disease progression or unacceptable toxicity); 28-day cycles Isatuximab: 10mg/kg IV; D1 Lenalidomide: 25mg PO; D1-21</p>
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Note:

1. A lower starting dose of lenalidomide is required for all patients with CrCl≤60ml/min
2. Dexamethasone dose reduced to 20mg weekly for patients >75 years of age (and/or uncontrolled diabetes). Dexamethasone dose should also be attenuated (10-20mg weekly) based on IMWG frailty stratification.

Dara-Rd: Daratumumab, lenalidomide and dexamethasone; Rd: Lenalidomide and dexamethasone; VRd: Bortezomib, lenalidomide and dexamethasone; VCD: Bortezomib, cyclophosphamide and dexamethasone; Vd: Bortezomib and dexamethasone; Dara-VRd: Daratumumab, bortezomib, lenalidomide and dexamethasone; Isa-VRd: Isatuximab, bortezomib, lenalidomide and dexamethasone.

Table Four

Suggested upfront dose adjustments as per frailty stratification^{2,3}

	IMWG-FI:†	FIT	INTERMEDIATE-FITNESS OR FRAIL
Agent	Starting dose		
Bortezomib (subcutaneous route preferred over intravenous)	1.3mg/m ²		1.0-1.3mg/m ² weekly
Lenalidomide	25mg		10-15mg‡
Dexamethasone (weekly)	20-40mg		10-20mg
Cyclophosphamide (weekly)	300mg/m ²		150mg/m ²

† <http://www.myelomafrailtyscorecalculator.net/>

‡ Older patients are more susceptible to lenalidomide-induced myelosuppression due to renal impairment, Suggest close monitoring at commencement of treatment and prompt dose reduction in event of toxicity. A lower starting dose is required for all patients with CrCl≤60ml/min.

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