

CLINICAL PRACTICE GUIDELINE

Treatment of patients with relapsed refractory multiple myeloma

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Introduction

The treatment landscape for multiple myeloma (MM) is undergoing a paradigm shift, with immune-based therapies moving into frontline settings. This evolution brings the possibility of achieving an operational cure (defined as a state of deep, sustained remission where survival approximates that of the age-matched general population), driven by the achievement of sustained minimal residual disease (MRD) negativity. However, despite significant advances, MM remains a largely incurable malignancy.

In Australia, current first-line therapies incorporating bortezomib and/or lenalidomide achieve a median progression-free survival (PFS) of approximately three years in transplant-eligible (TE) patients and around two years in those who are transplant-ineligible (TIE), according to the Australian and New Zealand Myeloma and Related Diseases Registry (<https://www.mrdr.net.au/>). The addition of front-line daratumumab has since improved outcomes. In TIE patients with newly diagnosed multiple myeloma (NDMM), the MAIA study¹ demonstrated a median PFS of about five years with DRd (daratumumab, lenalidomide, and dexamethasone), which is reimbursed in Australia. Among TE patients, the PERSEUS trial² reported a 4-year PFS rate of 84% with daratumumab-based quadruplet therapy. Despite these improvements, most patients ultimately experience disease relapse.

"Relapsed MM" refers to disease progression after a prior response that necessitates the initiation of new therapy. "Refractory MM" is defined as disease progression either during treatment or within 60 days of stopping the most recent therapy, provided the patient had achieved at least a minor response. "Primary refractory MM" denotes the failure to achieve even a minor response to initial treatment³

While not all patients with relapsed myeloma require immediate treatment, those presenting with clinical relapse (**Box 1**, page 6) should begin therapy without delay. In patients without new or worsening CRAB symptoms, treatment should still be initiated if there is a rapid rise in paraprotein or serum free light chain (SFLC) levels (**Box 1**), to prevent irreversible end-organ damage. For patients with slow biochemical relapse and no clinical symptoms, a strategy of active surveillance may be considered until further progression occurs. However, emerging data from the ANZ MRDR (Gration B et al., ASH 2024) highlight that end-organ damage developing during biochemical relapse may be less reversible than previously thought, underscoring the importance of close monitoring.

Box 1 outlines the criteria for initiating treatment in patients with relapsed multiple myeloma.

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).

Indications to commence treatment for multiple myeloma at relapse⁴

Clinical Relapse

- Development of new soft tissue plasmacytomas or bone lesions
- Definite increased ($\geq 50\%$) size of existing plasmacytomas or bone lesions.
- Hypercalcaemia ($\geq 11.5\text{mg/dl}$; 2.875mmol/l)
- Decrease in haemoglobin by $\geq 20\text{g/L}$ or to $< 100\text{g/L}$ due to myeloma.
- Rise in serum creatinine by $> 177\ \mu\text{mol/L}$ (2mg/dL) due to myeloma.

Significant biochemical relapse prior to the onset of end organ damage

- Doubling of paraprotein in two consecutive measurements less than two months apart with at least a 5g/L absolute increase or
- Any of the following increases in two consecutive measurements:
 - The absolute level of paraprotein by $\geq 10\text{g/L}$ or
 - **The increase of urinary M protein (BJP) by $\geq 0.5\text{g}$ per 24 hours or**
 - **Increase of involved FLC level by $\geq 200\text{mg/L}$ (with abnormal K:L ratio) or 25% increase (whichever is greater).**

Treatment of patients with relapsed refractory multiple myeloma

Relapsed/refractory multiple myeloma (RRMM) is treated using a variety of drug classes, including immunomodulatory drugs (IMiDs: lenalidomide, pomalidomide, and, less commonly, thalidomide), proteasome inhibitors (PIs: bortezomib, carfilzomib), anti-CD38 monoclonal antibodies (such as daratumumab), alkylating agents, anthracyclines, and corticosteroids. Selected patients may also be considered for high-dose melphalan followed by autologous stem cell transplantation (ASCT). These therapies can be used in different combinations and sequences, often within the reimbursement constraints of the Pharmaceutical Benefits Scheme (PBS) (www.pbs.gov.au). However, no universally accepted treatment sequence exists (**see Figure 1, Box 1, Table 2**).

It is important to note that many regimens considered standard and acceptable in relapsed/refractory myeloma internationally may not be approved by the Therapeutic Goods Administration (TGA) or reimbursed by the PBS in Australia. For agents that are neither TGA-approved nor PBS-reimbursed, access is only possible through private purchase facilitated via the Special Access Scheme (SAS). For agents that are TGA-approved but not PBS-reimbursed, access can occur through standard private purchase. PBS-approved regimens, which are reimbursed, remain the most commonly used in clinical practice in Australia.

Table 3 outlines commonly used RRMM regimens and specifies their TGA approval and PBS reimbursement status.

General Treatment Principles

Enrolment in a clinical trial is strongly recommended when available. Otherwise, the following principles guide treatment:

→ **Switch Drug Class:** When selecting a salvage regimen for relapsed/refractory multiple myeloma (RRMM), switching to a different drug class is generally preferred. However, using an alternative agent within the same class as the drug on which the patient progressed may still be appropriate, particularly when combined with a drug from a different class. Retreatment with a previously used regimen to which the patient was not refractory may be considered if a durable prior response was achieved—typically defined as a treatment-free interval of more than 12 months—and if the regimen was well tolerated without significant toxicity. Nonetheless, the depth or duration of response with retreatment is often reduced

→ **Salvage High-Dose Therapy (HDT) and ASCT:** This approach can be considered for patients who previously achieved a deep and durable response (e.g., \geq PR) to this approach. In accordance with International Myeloma Working Group recommendations, a second ASCT is not advised for patients whose response to the first ASCT lasted less than 3 years (or less than 2 years if no post-ASCT maintenance was given)⁵

→ **Rapidly Progressive Disease:** Use regimens combining an IMiD and/or PI with a monoclonal antibody or chemotherapy (see **Table 2**). Triplet combinations are more effective than doublet regimens. In patients with proliferative and heavy burden disease, debulking chemotherapy and/or radiotherapy may be required in addition.

→ **Slow Progressive disease:** For patients with a slower relapse tempo, minimising side effects is important. In cases where triplet combination therapy is not well-tolerated, doublet regimens—such as a proteasome inhibitor (PI) or an immunomodulatory drug (IMiD) combined with dexamethasone—may be suitable. Alternatively, close observation may be appropriate for frail or elderly patients, especially in the absence of end-organ damage.

→ **Exhausted Treatment Options:** After all novel agents and combinations are used, conventional-dose cyclophosphamide, low-dose melphalan, or corticosteroids may be viable options. Palliative care is appropriate for patients unable to tolerate further treatment (see **Box 2**).

Considerations Based on Co-Morbidities

→ **Pre-existing Neuropathy:** Use bortezomib or thalidomide cautiously or avoid if alternatives are available.

→ **Thrombosis Risk:** Patients with a history of venous thromboembolism (VTE) or high VTE risk require prophylactic or therapeutic anticoagulation with IMiDs. VTE risk is highest with high-dose dexamethasone or anthracycline-based regimens.

→ **Renal Impairment:** Proteasome inhibitors can be used in patients with renal impairment; carfilzomib is feasible even in those requiring dialysis, with close monitoring for complications (REF). Among IMiDs, lenalidomide—being primarily renally excreted—requires dose adjustment in moderate-to-severe renal impairment, whereas thalidomide and pomalidomide are less affected by renal clearance. Among immunotherapies, anti-CD38 monoclonal antibodies (e.g., daratumumab, isatuximab) and BCMA-targeted T-cell engagers (e.g., teclistamab, elranatamab) can be used in renal impairment, including dialysis-dependent patients, with careful monitoring. Similarly, belantamab mafodotin may be used, although data in severe renal impairment is limited. Mild-to-moderate impairment does not significantly alter the pharmacokinetics of immune therapies, and small case series of BsAb T cell engagers and belamaf suggest it may be well tolerated and safe in dialysis, but prospective data is lacking.⁶

→ **Uncontrolled Hypertension:** Control hypertension (e.g., to $\leq 140/90$ mmHg) before initiating carfilzomib therapy. Blood pressure should be monitored throughout treatment.

→ **Pulmonary or Cardiac Conditions:** Carfilzomib should be used cautiously in patients with pulmonary hypertension or uncontrolled cardiac disease.

Choice of Salvage regimens for the treatment of patients with relapse refractory multiple myeloma

Traditionally, the number of prior lines of therapy was used to define how heavily pretreated a patient is. However, this has become less informative with the early use of triplet and quadruplet regimens in front-line, meaning patients with fewer prior lines may already be refractory to multiple drug classes—a marker of poorer prognosis. The prospective LocoMMotion study demonstrated that triple-class exposed patients treated with standard-of-care salvage regimens had a median PFS of 4.6 months and OS of 12.4 months, underscoring the relevance of drug class exposure as a more meaningful measure of treatment intensity.⁷

Double-class exposed/refractory typically refers to resistance to IMiDs and PIs; triple-class includes anti-CD38 monoclonal antibodies; and quad-class reflects additional exposure or resistance to anti-BCMA therapies. Penta-drug exposed/refractory usually refers to prior exposure to at least two IMiDs, two PIs, and an anti-CD38 mAb. Despite this shift in clinical relevance, some PBS restrictions for salvage regimens continue to reference the number of prior therapy lines—an approach increasingly out of step with modern treatment paradigms.

In Australia, PBS-reimbursed treatment regimens for patients who have relapsed after first-line therapy include: Dara-Vd (daratumumab, bortezomib, and dexamethasone, reimbursed exclusively for second-line use), Kd (carfilzomib and dexamethasone), KRd (carfilzomib, lenalidomide, and dexamethasone), KTd (carfilzomib, thalidomide, and dexamethasone), PVd (pomalidomide, bortezomib, and dexamethasone), Pd (pomalidomide and dexamethasone), and SVd (selinexor, bortezomib, and dexamethasone) or Sd (selinexor and dexamethasone).

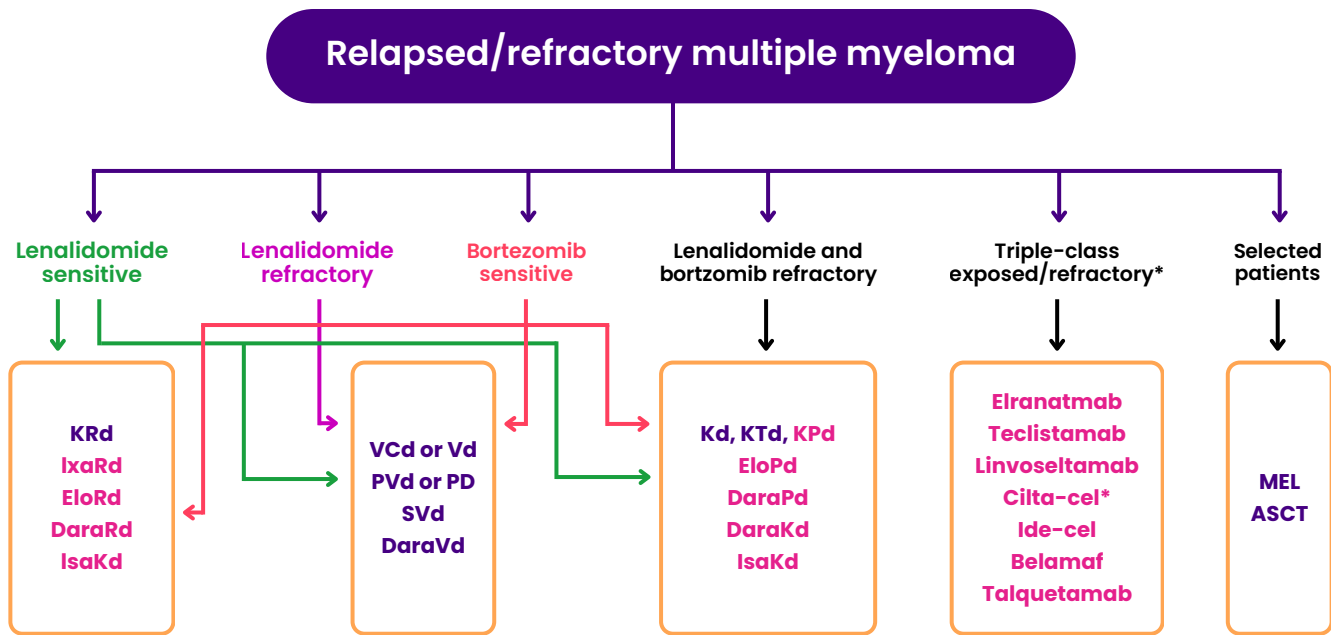
As of July 2025, the Pharmaceutical Benefits Advisory Committee (PBAC) has recommended elranatamab (Elrexfio®) for the treatment of patients with relapsed or refractory multiple myeloma (RRMM) who are triple class exposed and have received at least three prior lines of therapy. Additionally, the Medical Services Advisory Committee (MSAC) has recommended public funding for ciltacabtagene autoleucel (cilta-cel), a BCMA-targeted CAR-T cell therapy, for triple-class exposed patients who have received at least four prior lines of therapy.

When selecting a salvage regimen at relapse, the general principle is to use the most effective and accessible therapy first, rather than reserving it for later lines. This is because patients may not survive long enough to receive subsequent treatments, and in any case, therapies tend to be more effective when used earlier in the treatment course. The optimal regimen at relapse varies between patients and should be guided by several factors, including comorbidities, frailty, the tempo of disease relapse, and prior drug exposure or refractoriness. In Australia, most patients at first relapse will have had prior exposure to lenalidomide, and many will be lenalidomide-refractory—a factor associated with poorer outcomes with currently available salvage options, and one that must be carefully considered when choosing therapy.

Figure 1 outlines the available treatment options for patients with relapsed/refractory multiple myeloma. **Table 2** summarises median progression free survival of IMiD/PI-based regimens in lenalidomide-refractory myeloma. It is important to note that direct comparisons between studies are not possible due to confounding factors, including differences in baseline patient characteristics.

Figure One

Therapy Selection in Relapsed/Refractory Myeloma: Algorithms Based on Prior Exposure and Globally Approved Combinations
(See table 3 for a list of salvage regimens for RRM)



V=Velcade (bortezomib), R=Revlimid, T= Thalidomide, d=dexamethasone, C=Cyclophosphamide, MEL = Melphalan, K = Carfilzomib, Ixa =Ixazomib, Elo = Elotuzumab, Dara =Daratumumab, Pom = Pomalidomide, S =Selinexor, Isa = Isatuximab

*Cilta-cel has received positive MSAC recommendation as of June 2024.

- Regimens reimbursed by Australian Pharmaceutical Benefit Scheme (PBS).
- Regimens approved internationally but not reimbursed by the Australian PBS

Table Two

Progression free survival of IMiD/PI-Based Regimens in Lenalidomide-Refractory Myeloma

Combination	Trial Name	PFS in the investigational arm					
		Len-naïve		Len-exposed		Len-refractory	
Lenalidomide-based		n	mPFS,Mo	n	mPFS,Mo	n	mPFS,Mo
KRd	ASPIRE	317	28.7	79	19.4	-	-
DRd	POLLUX ²	286	45	50	38.9	0	NA
Bortezomib or Carfilzomib-based		n	mPFS,Mo	n	mPFS,Mo	n	mPFS,Mo
Kd	ENDEAVOR	287	22.2	177	12.9	113	8.6
DKd	CANDOR	189	28.4	123	25.9	99	28.1
DVd	CASTOR	251	16.7	89	9.5	60	7.8
IsaKd	IKEMA	107	-	72	-	57	15.7
SVd	BOSTON	NA	NA	77	NR	53	10.2
Pomalidomide-based		n	mPFS,Mo	n	mPFS,Mo	n	mPFS,Mo
PVd	OPTIMISMM	0	NA	281	11.2	200	9.5
EloPd	ELOQUENT-3	1	NA	59	10.3	54	10.2
IsaPd	ICARIA	0	NA	154	11.5	144	HR 0.59

Cross-studied comparisons are not valid due to confounding factors, including differences in the baseline characteristics of enrolled patient populations

■ Regimens reimbursed by Australian Pharmaceutical Benefit Scheme (PBS)

■ Regimens approved internationally but not reimbursed by the Australian PBS

Dara-Vd is reimbursed by the PBS only for patients who have had 1 prior line of therapy, based on the phase III CASTOR study⁸ in which DVd was superior to Vd with respect to PFS (16.7m vs. 7.1m, HR 0.31 p<0.0001). The PFS benefit was most apparent at 1st relapse (NR vs. 7.9m, HR 0.19, p<0.0001). Unlike the OPTIMISMM⁹ study in which bortezomib was given until disease progression with PVd, bortezomib with DVd was only given for 8 cycles, followed by daratumumab monotherapy until disease progression in the CASTOR study. Nonetheless, peripheral neuropathy was frequent though not severe (all grade, 49.8%; grade≥3, 4.5%). Thus, as with PVd, consider using subcutaneous weekly bortezomib to minimise the risk of peripheral neuropathy. As with the OPTIMISMM study, the CASTOR study excluded patients who were refractory to bortezomib, in whom DVd is not the salvage therapy of choice.

Kd is reimbursed under the PBS for patients who have received at least one prior line of treatment. This is based on the phase III *Endeavor* study, which demonstrated Kd's superiority over bortezomib and dexamethasone (Vd) in terms of progression-free survival (PFS, HR 0.53, p<0.0001) and overall survival (OS, HR 0.79, p=0.01)¹⁰. In the *Endeavor* trial, carfilzomib was administered at a dose of 20/56 mg/m² (20 mg/m² on cycle 1, day 1, then 56 mg/m² starting cycle 1, day 8) using the standard twice-weekly schedule (days 1, 2, 8, 9, 15, and 16) within a 28-day cycle. The phase III *ARROW* study investigated a once-weekly regimen of carfilzomib (20/70 mg/m²: 20 mg/m² on cycle 1, day 1, then 70 mg/m² starting cycle 1, day 8). It found this regimen to be as effective as the twice-weekly 20/27 mg/m² schedule in terms of response rates and PFS, with an improved safety profile. The relative benefit of Kd over Vd was most pronounced in patients with one prior line of treatment (*median PFS*: 22 months vs. 10 months, HR 0.447, p<0.001). Significant benefits were also observed in patients who were: 1. Previously exposed to bortezomib (*median PFS*: 10.6 months vs. 8.1 months, HR 0.688, p=0.0052), 2. Lenalidomide-exposed or refractory (*median PFS*: 12.9 months vs. 7.3 months, HR 0.688, p=0.0052).¹¹

The addition of cyclophosphamide to Kd (**KCd**) is safe and effective and tends to benefit patients with prior lenalidomide refractoriness.¹² Continuation of Kd beyond the initial 6 cycles of KCd for 18 months induced better PFS than no maintenance (from start of maintenance, 11.9 vs. 5.6m, HR 0.59, p=0.0086).¹³

KRd is reimbursed on PBS in Australia for patients in 2nd line therapy and beyond. In the ASPIRE study, KRd induced a superior PFS compared with Rd (HR 0.69, p <0.001).¹⁴ Importantly, the ASPIRE study did not enrol patients who were refractory to lenalidomide, as is the case for most Australians with RRMM. Lenalidomide-naïve patients had a much longer PFS (med 28.7m) patients with prior lenalidomide exposure (med 19 months).

KTd is an acceptable triplet combination when the use of lenalidomide is limited by renal impairment. In the Australian ALLG MM018 study, KTd demonstrated high ORR (82%; ≥VGPR 65%; CR 16%) with a median PFS of 23 months.¹⁵

The most common side effects of carfilzomib are hypertension (14% grade≥3), fatigue (7% grade≥3), dyspnoea (6% grade≥3), anaemia and thrombocytopenia which are all manageable. In the *Endeavor* study, cardiac failure was more common in the carfilzomib arm (all grade ~6% vs. ~2% (Vd)).

PVd is reimbursed by the PBS for patients who have had at least 1 prior lenalidomide-containing line of treatment, based on results of the phase III OPTIMISMM study that demonstrated its superiority to Vd with respect to PFS (med 12.2m vs. 7.1m (Vd), HR 0.61, $p < 0.0001$).⁹ On Sub-analysis, the degree of superiority of PVd over Vd was similar whether PVd was used in early or late-line relapse (HR 0.54 in patients with 1 prior line and 0.6 in patients with >2 prior lines). Importantly, in the OPTIMISMM study, all patients had prior lenalidomide-exposure, 70% of whom were lenalidomide-refractory, which reflects the Australian patient-population at first relapse. However, this study excluded patients who were refractory to bortezomib, for whom PVd is not the regimen of choice. Approximately 25% of patients stopped treatment due to adverse events, mainly peripheral neuropathy. Thus, in patients who are at risk of peripheral neuropathy, consider using subcutaneous weekly bortezomib. In a phase II study, PCd (pomalidomide, cyclophosphamide, and dexamethasone) achieved a median PFS of 13 months¹⁶ and may be considered for patients who are unable to tolerate bortezomib because of peripheral neuropathy. The use of **Pd** (Pomalidomide and dexamethasone) can be expected to result in a modest median PFS of 4 months in patients with RRMM based on the phase III MM003 study¹⁷.

SVd is PBS-subsidised for patients with RRMM based on the phase 3 BOSTON study that compared selinexor, bortezomib, and dexamethasone (SVd) with bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma.¹⁸ SVd significantly improved median progression-free survival (13.93 vs. 9.46 months) and enabled once-weekly bortezomib dosing, reducing peripheral neuropathy. However, selinexor was associated with increased gastrointestinal toxicity, including nausea, vomiting, anorexia, diarrhea, and weight loss, which are generally manageable but may require dose adjustments. Please refer to the MSAG supportive guideline for the use of selinexor.

There are several other effective triplet combinations for a patients with RRMM which are based on combinations of IMiDS, PIs and anti-CD38mAb that are *not reimbursed by the Australian PBS*. A non-exhaustive list of these regimens are summarised in **table 3**.

BCMA-targeted therapies

BCMA-targeted therapies represent the fourth major treatment backbone for relapsed or refractory multiple myeloma (RRMM), following immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies. They are especially important for patients who are triple-class exposed, a group with limited options and poor outcomes. This class includes CAR-T cell therapies—ciltacabtagene autoleucel (Cilta-cel; Carvykti®) and idecabtagene vicleucel (Ide-cel; Abecma®); bispecific T-cell engagers (TCEs)—teclistamab (Tecvayli®), elranatamab (Elrexio®), and linvoseltamab (Linozyfic®); and the BCMA-targeted antibody-drug conjugate belantamab mafodotin (Blenrep®). As of January 2026, the BCMA-targeted therapies that are TGA approved and may soon be publicly funded in Australia are Ciltacel, Elranatmab and Teclistmab.

Cilta-cel received a positive MSAC recommendation for use in triple-class exposed patients with relapsed/refractory multiple myeloma who have received at least four prior lines of therapy, based on results from the phase 1b/2 CARTITUDE-1 study.¹⁹ In this trial, which enrolled heavily pretreated patients (median of six prior lines), ciltacabtagene autoleucel (cilta-cel) achieved a median overall survival of 60.7 months at a median follow-up of 61.3 months, with 33% of patients remaining progression-free without further therapy for ≥5 years. The most common side effect was cytokine release syndrome (CRS), seen in ~95% of patients, usually grade 1–2; grade ≥3 CRS was rare (~4%), with onset around day 7 and resolution within two weeks. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in about 16% of patients, mostly mild. A small subset (~5%) experienced delayed movement and neurocognitive treatment-emergent adverse events (MNTs), such as parkinsonism, cognitive decline, and personality changes, typically emerging after CRS/ICANS resolution. These rare but serious effects were associated with high tumour burden, significant CRS, ICANS, and robust CAR T-cell expansion. While their incidence has decreased in later studies through mitigation strategies, their reversibility and optimal management remain under investigation.

Elranatamab received a positive PBAC recommendation based on the phase 2 MagnetisMM-3 trial in triple-class BCMA-naïve RRMM patients.²⁰ Elranatamab demonstrated ORR of 61%, with 35% achieving CR or better. After a median follow up of just over 28 months, the median PFS was 17.2 months (95% CI, 9.8–not-estimable [NE]) and the median OS was 24.6 months (95% CI, 13.4–NE). CRS occurred in 58% of patients, mainly grade 1–2 severity. Infections occurred in nearly 70%, including a significant proportion of grade 3–4 events. Transitioning responding patients to biweekly dosing reduced the incidence of severe adverse events.

Teclistamab is approved by the TGA in Australia but not yet PBS-reimbursed. The approval was based on the MajesTEC-1 phase 1/2 study in triple-class exposed RRMM patients, which showed a 63% overall response rate with 39% achieving complete response or better.²¹ At a median follow-up of about 30 months, the median progression-free survival was 11.3 months, while median duration of response and overall survival were not reached, with an estimated 74% overall survival among responders. Common side effects included mostly mild cytokine release syndrome (60–70%), ICANS (~6%), and infections.

Due to the high risk of hypogammaglobulinemia and infections with continuous therapy of BCMA-targeted BsAb TCE, management requires careful attention to immunoglobulin (Ig) replacement and prophylaxis against *Pneumocystis jirovecii* pneumonia using trimethoprim–sulfamethoxazole, as well as varicella-zoster virus prophylaxis with valacyclovir.

Refer to page 17 for agents with regulatory approval in countries other than Australia.

Access of therapeutic agents on compassionate access programs

Compassionate access programs enable some pharmaceutical industries to offer new drugs that have some evidence to support their clinical use but are either not TGA (Therapeutic Goods Administration) approved or PBS-reimbursed to patients when no other treatments are available. Pharmaceutical industries are not required to provide their medications for compassionate use, however, they will publicly post contact information for compassionate drug requests.

BOX TWO

Recommendation for the treatment of relapsed multiple myeloma

There is no standard treatment sequence for relapsed multiple myeloma (MM). Management should be individualized based on prior therapies and their toxicities, depth and duration of previous response, disease tempo, and the patient's current fitness.

The most effective available treatment should be used early, rather than reserved for later lines of therapy.

- Indications to initiate treatment are outlined in **Box 1**.
- Treatment algorithms by prior therapy exposure are shown in **Figure 1**.
- Common regimens for relapsed/refractory MM (RRMM) are listed in **Table 3**.

Clinical trial enrolment is strongly recommended when available.

Switching to a different drug class is generally preferred. However, substituting another agent within the same class may be reasonable, especially in combination with a drug from a different class.

Retreatment with a prior regimen may be considered if the patient was not refractory, had a durable prior response (typically ≥ 12 months off therapy), and previously tolerated the regimen well. Responses in this setting are often shorter and less deep (Grade C recommendation).

A second autologous stem cell transplant (ASCT) may be considered for selected patients who achieved at least a partial response with a remission lasting >3 years (>2 years if no post-ASCT maintenance was given) (Grade B recommendation; Level 4 evidence).

If novel therapies and combinations have been exhausted, traditional options—such as moderate-dose cyclophosphamide, non-myeloablative melphalan, or low-dose corticosteroids—may be used. Palliative care should be offered to patients unfit for further treatment (Grade C recommendation).

Agents used in RRMM that are not reimbursed by the Australian Pharmaceutical Benefit Scheme

Treatment options for multiple myeloma (MM) have rapidly expanded with the emergence of novel, effective therapies. However, access remains a major challenge in Australia due to affordability and funding constraints.

Australia's national healthcare system provides subsidised care via Medicare and the Pharmaceutical Benefits Scheme (PBS). While Therapeutic Goods Administration (TGA) approval is required for PBS listing, it often lags behind U.S. FDA approval. Unlike the U.S. insurance-based model, Australia provides universal access to affordable medicines which results in different access timelines.

Below is a non-exhaustive list of promising therapies that have received regulatory approval in other countries, but are currently not TGA-approved or reimbursed by the PBS. These include:

Anti-CD38mAb:

Isatuximab (Sarclista®): Isatuximab is another mAb against CD38, that has similar mechanism of action to daratumumab. Isatuximab in combination in combination with pomalidomide and dexamethasone (IsaPd), or carfilzomib and dexamethasone (IsaKd) are TGA-approved for the treatment of patients with relapsed myeloma. The PFS of patients in the IsaPd and IsaKd arms were superior to their respective Pd (HR 0.59, $p=0.001$) and Kd (HR 0.53, $p=0.0007$) control arms in the ICARIA-MM²² and IKEMA²³ studies, respectively.

BCMA-targeted therapies:

Belantamab mafodotin (Belamaf; Blenrep®): Belamaf is a BCMA-targeted antibody-drug conjugate that delivers the cytotoxic agent MMAF to malignant plasma cells. In addition, it retains antibody-dependent cellular cytotoxicity (ADCC) activity, enhancing immune-mediated killing of myeloma cells. In RRMM, the phase III DREAMM-7 trial (Belamaf + bortezomib + dexamethasone, BVd) showed a 42% reduction in risk of death compared to daratumumab-based therapy, with 3-year overall survival rates of 74% vs 60%.²⁴ DREAMM-8 (Belamaf + pomalidomide + dexamethasone, BPd) demonstrated a 48% reduction in risk of progression vs PVd, with a favourable trend in overall survival.²⁵ These combinations are approved in Europe and the UK after at least one prior therapy but as of July 2025, they are not yet TGA-approved or PBS-reimbursed in Australia.

Linvoseltamab (Lynozytic®): Linvoseltamab is a BCMA-targeted BsAb TCE that redirects T-cell cytotoxicity toward myeloma cells. In the LINKER-MMI phase I/II trial of triple-class-exposed or refractory patients, the 200 mg dose achieved a 71% overall response rate, with ~50% achieving \geq CR.²⁶ Median duration of response was 29 months, and median overall survival was 31.4 months, with a manageable safety profile (CRS 46%, mostly grade 1–2; ICANS 8%). Linvoseltamab received conditional EMA approval (April 2025) for patients after \geq 3 prior lines and FDA accelerated approval (July 2025) for those after \geq 4 prior lines. As of July 2025, it is not TGA-listed or PBS-reimbursed in Australia.

Idecabtagene vicleucel (Ide-cel, Abecma®): Ide-cel is a BCMA directed CART cell therapy that is FDA approved for adults with relapsed or refractory multiple myeloma after at least two prior lines of therapy—including an IMiD, a proteasome inhibitor, and an anti CD38 agent. This approval was based on the phase III KarMMa 3 trial in which ide cel significantly improved median progression free survival (13.3 vs 4.4 months; HR 0.49; $P < 0.0001$), with higher overall response rates (71% vs 42%, including complete responses of 39% vs 5%) versus standard regimens.²⁷ Deeper, more durable responses were seen across all high risk subgroups, though grade 3/4 adverse events were common and included cytokine release syndrome (Grade ≥ 3 in ~5%) and neurotoxicity (Grade ≥ 3 in ~3%). In Australia, ide-cel has not received TGA approval and is not publicly funded.

GPRC5D-targeted therapies:

Talquetamab (Talvey®): Talquetamab is a BsAb TCE targeting GPRC5D on myeloma cells and CD3 on T-cells. In the MonumenTAL-1 trial of heavily pretreated relapsed/refractory myeloma (≥ 4 prior lines), it achieved overall response rates of ~73–74%, with a median duration of response of 9.5 months and two-year overall survival of 60–67%.²⁸ Adverse events involving skin and nails—reflecting GPRC5D expression in epithelial tissues—were common but generally manageable. Talquetamab received FDA accelerated approval and conditional EMA approval in August 2023 for patients with ≥ 4 and ≥ 3 prior lines of therapy, respectively. It is not yet TGA-approved or PBS-reimbursed in Australia.

Anti-BCL2:

Venetoclax is a BCL 2 inhibitor demonstrating remarkable efficacy in t(11;14) multiple myeloma with high BCL 2 expression. In a phase I trial, it achieved an overall response rate (ORR) of 86% in this subgroup. In the phase III BELLINI trial, venetoclax plus bortezomib and dexamethasone (VenVd) significantly improved progression-free survival (PFS) compared to Vd (HR 0.63, $p=0.01$), though infection-related mortality increased overall.²⁹ However, the benefit-risk balance was favorable in t(11;14) or high-BCL 2 patients [t(11;14): HR 0.11, $p=0.02$; high BCL 2: HR 0.34, $p=0.01$]. Although venetoclax has not been approved for multiple myeloma in any country, it is explicitly recommended in the NCCN Guidelines (U.S.) for relapsed/refractory t(11;14) myeloma patients. Additionally, the 2020–2021 EHA–ESMO Clinical Practice Guidelines for multiple myeloma in Europe advise evaluating t(11;14) status to guide venetoclax-based regimens when available in Europe. In Australia, venetoclax remains unregistered and not PBS-reimbursed for the treatment of myeloma.

Alkylating Agents:

Bendamustine (Treanda®, Bendeka®): Bendamustine is an alkylating agent with unique biochemical structure that confers both alkylating agent and nucleoside analogue activity, that result in both induction of apoptosis and inhibition of mitotic check points, as opposed to induction of necrosis alone as seen with other alkylators³⁰. In phase I and II trials, bendamustine was efficacious as monotherapy, and in combination with thalidomide, lenalidomide or bortezomib³¹. Combination bendamustine, bortezomib and dexamethasone was shown to induce an ORR of 68% (CR/VGPR 35.5%) and PFS of 9.7 months in a group of patients with a median 2 prior lines of treatment³². In Australia, bendamustine is not TGA listed or subsidised by the PBS for the treatment of multiple myeloma.

Table Three

Overview of Selected Therapeutic Options for Relapsed/Refractory Multiple Myeloma

*Comparing outcomes across clinical trials is limited by confounding factors, including variations in enrolled patient populations. Agents that are neither TGA-approved nor PBS-reimbursed can only be accessed via private purchase through the Special Access Scheme (SAS). Agents that are TGA-approved but not PBS-reimbursed may be obtained through standard private purchase. PBS-approved and reimbursed regimens remain the most commonly used in clinical practice in Australia.

Regimen	Study (Phase)	Prior LoT (median, range)	ORR (%)	Median PFS (mo)	OS (mo) or HR	TGA or PBS
POMALIDOMIDE-BASED						
Pom-dex	MM-003 (Phase III)	≥ 2	~33-35	≈ 12	OS benefit vs Hd-dex	PBS-funded
PCd	Phase II study	≥ 2	73	13.3	57 mo	PBS funded
PVd (pom-vel-dex)	OPTIMISMM (Phase III)	Len-exposed	≈ 82	~11.2	—	PBS-funded
D-Pd (dara-pom-dex)	APOLLO (Phase III)	≥ 1	~60-63*	~12-16	OS improved vs Pd	Not PBS funded TGA-approved
Isa-Pd (isatux-pom-dex)	ICARIA-MM (Phase III)	≥ 2	~60-63	~11	OS improved (≈ +6.9 mo)	Not PBS funded TGA-approved
Elo-Pd (elotuzumab-pom-dex)	ELOQUENT-3 (Phase II)	1-3	≈ 53-55	~10-11	Better OS vs Pd	Not PBS Funded nor TGA approved
LENALIDOMIDE BASED						
IRd (ixaz-len-dex)	TOURMALINE-MM1 (Phase III)	≥ 1	~78	20.6	OS ~53.6 mo	Not PBS funded TGA-approved
DRd (dara-len-dex)	POLLUX (Phase III)	1-3	~92	~44	OS benefit vs Rd (~77.8 mo)	Not PBS funded for RRMM TGA-approved
CARFILZOMIB BASED						
Kd (carfilz-dex)	CANDOR control arm	1-3	NA	~18-19	—	PBS-funded
KRd (carfilz-len-dex)	ASPIRE (Phase III)	~2	87.1	26.3	OS improved vs Rd	PBS-funded
KdD (dara-carfilz-dex)	CANDOR (Phase III)	1-3	~84	28.4	OS improved vs Kd	Not PBS funded TGA-approved
Isa-Kd (isatux-carfilz-dex)	IKEMA (Phase III)	~2 (range 1-3)	≈86-87	~35.7	—	Not PBS funded TGA-approved

SELINEXOR BASED						
SVd (selinexor–bortezomib–dex)	BOSTON (Phase III)	1–3	76%	13.9	NR at 28 mo follow up; HR 0.84	PBS-funded
BCMA-targeted BsAb TCE						
Teclistamab (BCMA-BsAb)	MajesTEC-1 (Phase I/II)	≥ 3	63	11.3	–	Not PBS funded Provisional TGA-approved as of Jan 2026
Elranatmab	MagnetisMM - 3	≥ 3 (BCMA naïve)	61	17.2	Med 24.6 mo	PBAC positive recommendation as of Apr2025; TGA-approved.
Linvoseltamab	LINKER MMI	≥ 3	71	NR at 21m in 200mg cohort	Med 31.4 mo	Not PBS funded Not TGA-approved
BCMA-targeted CAR-T cell						
Ide-cel (CAR-T)	KarMMa-3 (Phase III)	2–4 ; triple-class-exposed	~73‡	~13.3	HR 0.49 vs SOC	Not PBS funded Not TGA-approved
Cilta-cel (CAR-T)	CARTITUDE-4 (Phase III)	1–3; Len-refractory	~98§	Not reached	OS reduced death risk by 45%	MSAC positive recommendation as of Jun 2024; TGA-approved
BCMA targeted ADC						
Belamaf (BCMA-ADC) + Pd	DREAMM-8 (Phase II)	≥ 1; len-refractory enriched	77	NR; 12-mo PFS 71%	12-mo OS ~83%	– Not PBS funded TGA-approved
Belamaf + Kd	DREAMM-7 (Phase II)	≥ 1	83	36.6 mo	18-mo OS 84%	– Not PBS funded Not TGA-approved

Conclusion

The treatment of multiple myeloma (MM) is rapidly evolving, with increasing therapeutic complexity as new agents become available. The standard of care continues to shift and differs across countries, particularly as Australia's approach is shaped by what is reimbursed through the Pharmaceutical Benefits Scheme (PBS), which applies rigorous evidence-based and cost-effectiveness assessments. While MM has traditionally been considered incurable, the use of anti-CD38 monoclonal antibodies in upfront treatment—particularly in combination regimens—has transformed outcomes, raising the possibility of an operational cure (defined as long-term disease control without ongoing therapy) for selected patients. Survival is expected to continue improving as more novel therapies are approved and made accessible. The treatment guidelines developed by the Medical Scientific Advisory Group (MSAG) to Myeloma Australia are based on the best available evidence, local clinical experience, and PBS-listed therapies. Establishing a national consensus treatment algorithm will not only improve consistency of care across the country but also lay the foundation for future, locally relevant clinical research.

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.

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