MEDICAL SCIENTIFIC ADVISORY GROUP (MSAG)
TO MYELOMA AUSTRALIA (MA)

Clinical Practice Guideline
MULTIPLE MYELOMA

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Myeloma Australia

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1 INTRODUCTION

Multiple myeloma (MM) is a malignancy of plasma cells characterised by an abnormal serum and /or urine immunoglobulin or free immunoglobulin light chain as a result of clonal expansion of plasma cells. It is often accompanied by complications of enhanced bone loss associated with diffuse osteopenia or focal lytic lesions, renal failure, hypercalcaemia, immune suppression and anaemia. In Australia, it is estimated that just over 2400 new cases were diagnosed in 2021, with one of the highest age-standardised incidence rates internationally at 7.6 cases per 100,000 persons which has increased from 6.8 cases per 100,000 persons in 2017 [1].

Over recent years, the number of approved therapeutic agents for the treatment of MM have expanded globally. In addition to proteasome inhibitors (*PI; bortezomib [Velcade®], carfilzomib [Kyprolis®] and ixazomib [Ninlaro®])*, immunomodulatory drugs *(IMiDs: thalidomide [Thalomid®], lenalidomide [Revlimid®] and pomalidomide [Pomalyst®])* and monoclonal antibodies *(mAb; elotuzumab [Empliciti®], daratumumab [darzalex®] and isatuximab [Sarclista®])*, agents from new therapeutic classes that are approved by the US FDA (Food Drug Administration) include immune drug conjugates *(ADC; Belantamab Mafodotin [Blenrep®])*, Chimeric Antigen Receptor-T cell therapies *(CAR-T; idecabtagene vicleucel [Abecma®], ciltacabtagene autoleucel (pending FDA-approval as of November 2021)*, and selective inhibitor of nuclear export *(SINE; selinexor [Xpovio®])*. Other emerging novel drug-classes that are verging entry into the clinics include Bispecific Antibody T or NK cell Engagers, Bcl-2 inhibitors *(eg. Venetoclax [venclexta®]),* and cereblon E3 ligase modulators (CELMoDs®)

Although drug access may vary between different parts of the world, there are common treatment principles that guide treatment. The following guideline for the effective treatment of MM focusses on drugs that are either reimbursed or can be accessed through other avenues in Australia. This guideline is a consensus established by the Medical Scientific Advisory Group (MSAG) to Myeloma Australia, which consists of a panel of haematologists across Australia. Levels of evidence and grades of recommendations in this guideline are as outlined in table 1

Table 1: Level of evidence and grades of recommendations.

LEVELS OF EVIDENCE	
1A	Evidence from meta-analysis of randomised control 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)

2 DIAGNOSTIC CRITERIA

The diagnosis of MM is usually confirmed by demonstrating the presence of a paraprotein in serum and/or urine with increased bone marrow plasma cells[2]. There are two phases that precede MM: An initial premalignant phase termed monoclonal gammopathy of uncertain significance (MGUS), followed by smouldering (or asymptomatic) MM (SMM). MM is now defined by the presence of myeloma defining events including end organ damage (specifically hypercalcaemia, renal impairment, anaemia and bone lesions (CRAB features) and/or the presence of three specific biomarkers (so called SLiM CRAB criteria) in people with no CRAB features including: clonal bone marrow plasma cells ≥ 60%, serum free light chain (FLC) ratio ≥ 100 (provided involved FLC level is ≥ 100 mg/L), or more than one focal lesion on MRI (Table 3).

Multiple myeloma is almost always preceded by MGUS[2]. Table 2 and 3 outline the criteria for the diagnosis of MGUS, smouldering and symptomatic MM.

Patients with SMM have a diverse clinical course, with a risk of progression to MM of approximately 10% per year in the first five years, 3 percent per year in the next 5 years, then 1 percent per year thereafter [3]. High risk smouldering myeloma (HR SMM) refers to the subgroup with an estimated risk of progression to MM of approximately 50% in the first 2 years. There are a number of models used to define HR SMM including the Mayo 2008 (≥10% bone marrow plasma cells, paraprotein of ≥30g/L and serum FLC ratio <0.125 or > 8)[4], the Spanish (≥10% bone marrow plasma cells, ≥95% plasma cells demonstrated to be clonal on flow cytometry and immunoparesis), and the Mayo 2018, 2/20/20 model which has been validated using a large cohort of almost 2000 patients meeting the revised IMWG criteria for SMM, to now be adopted as in the International Myeloma Working Group (IMWG), 2/20/20 model (table 4). People with 2 to 3 risk factors as outlined by the IMWG 2/20/20 model are considered to have HR SMM, with a 2 years risk of progression to MM of approximately 45%. In addition, the presence of any one of the FISH/cytogenetic abnormalities including t(4;14), t(14;16), +1q, del17p, or del13q/monosomy 13 conferred an additional risk factor for progression to MM[3, 5]

Table 2: Diagnostic criteria according to the International Myeloma Working Group 2014[2].

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)	SMOULDERING MYELOMA	MULTIPLE MYELOMA
FLC ratio (<0.26 or >1.65) in the absence of Ig heavy chain expression on immunofixation with increased level of the appropriate involved light chain (increased κ FLC in patients with ratio >1.65 and increased λ FLC in patients with ratio <0.26) - Bone marrow clonal plasma cells <10% in the aspirate, and low level of plasma cell infiltration in the trephine. - Absence of myeloma defining events (table 3). - No evidence of other B-cell lymphoproliferative disease (LPD) or light chain associated amyloidosis or other light chain, heavy chain or immunoglobulin associated tissue damage.	- Serum paraprotein ≥30g/l or urinary monoclonal protein ≥500 mg per 24 hours and/or bone marrow clonal plasma cells 10-60%. - Absence of myeloma defining events (table 3) - No evidence of amyloidosis	Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma **and** presence of Myeloma defining events (table 3).

Table 3: Myeloma defining events.

END ORGAN DAMAGE (CRAB)	
C-Increased calcium level	Corrected serum Calcium >0.25mmol/l above the upper limit of normal or >2.75mmol/l
R-Renal insufficiency	Creatinine clearance <40 mL per min or serum creatinine >177 μmol/L (>2 mg/dL)
A-Anaemia	Hb <100g/L or 20g/L below the lower limit of normal
B-Bone lesions	One or more osteolytic lesions on skeletal radiography, CT, or PET-CT
BIOMARKERS OF MALIGNANCY (SLiM-CRAB criteria)	
Clonal bone marrow plasma cell percentage* ≥60%	
Involved:uninvolved serum free light chain ratio** ≥100	
>1 focal lesion on MRI studies***	

* Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence.

** These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.

*** Each focal lesion must be 5 mm or more in size.

Table 4: IMWG 2/20/20 model for risk stratification of smouldering myeloma[3]

Risk factors*		
Serum M-protein >2g/dL		
Involved to uninvolved free light-chain ratio >20		
Marrow plasma cell infiltration >20%		
Number of risk factors	**Risk Stratification Group**	**Risk of progression to MM (2 years)**
0	Low risk	6.2%
1	Intermediate risk	17.9%
2-3	High risk	44.2%

* The presence of any one of the FISH/cytogenetic abnormalities including t(4;14), t(14;16), +1q, del17p, or del13q/monosomy 13 conferred an additional risk factor for progression to MM.

2.1 THE ROLE OF PROGNOSTIC MARKERS

The natural history of MM can vary markedly between patients; survival can range from several months, to many years. Genetic heterogeneity and disease biology across different patients and even between different myeloma clones within the same patients with MM is vast, and currently, the implication this has to therapy is still poorly defined. Nonetheless, using commonly available prognostic markers (table 6), a group of crudely defined high-risk patients can be identified that can in turn impact on treatment decisions. By definition, patients with high-risk MM are considered those with an OS of 2 years or less despite treatment with IMiDs and proteasome inhibitors[6].

Currently, the most widely adopted prognostic model is the revised international staging system (R-ISS; table 5). This model is based on the traditional ISS that incorporates serum levels of $\beta_2$microglobulin (β_2M) and albumin, as well as LDH and high-risk FISH (del17p and t(4;14)) [7]. The R-ISS risk stratification system identifies 3 different MM prognostic groups in patients who were treated in the era of IMiDs and proteasome inhibitors and supersedes the conventional ISS staging system.

A number of molecular methods for risk stratification have emerged in recent years such as gene expression profiling, SNP (single nucleotide polymorphism)-based mapping arrays and comparative genomic hybridisation. At present, these techniques are only used in the setting of clinical trials.

Table 5: Revised International Staging System [7].

REVISED INTERNATIONAL STAGING SYSTEM (R- ISS)			
Stage	**Criteria**	**Med OS***	**5 Year OS**
R-ISS I	- ISS I (Serum ß2M <3.5mg/l and serum Albumin >35g/l) *AND* - Normal LDH *AND* - No high-risk FISH profile (defined as del17p and/or t(4;14) and/or t(14;16))	NR	81%
R-ISS II	Patients failing to meet criteria for R-ISS I or III.	83m	62%
R-ISS III	ISS III (Serum ß2 microglobulin >5.5mg/L) *AND* High risk FISH OR High LDH	43m	39%

*** Note the OS quoted for ISS and R-ISS are derived in different eras and are therefore not comparable between the two prognostic systems.**

Table 6: Factors associated with poorer prognosis in multiple myeloma.

HIGH RISK FACTORS	The following tests for high-risk disease are routinely available in Australia and are recommended.
ISS (international stage system) III (Serum ß2 microglobulin >5.5mg/L) **Conventional Cytogenetics** - Del17p - Hypodiploidy - Deletion of chromosome 13[1] **Fluorescent in situ hybridisation (FISH)** - t(4;14) - t(14;16) - Del17p - 1q21 amplification **High lactate dehydrogenase (LDH)**	ß2 microglobulin Albumin **Conventional Cytogenetics **** **Fluorescent in situ hybridisation (FISH)[2]** - t(4;14) - t(14;16) - Del 17p - 1q21 amplification. **LDH**

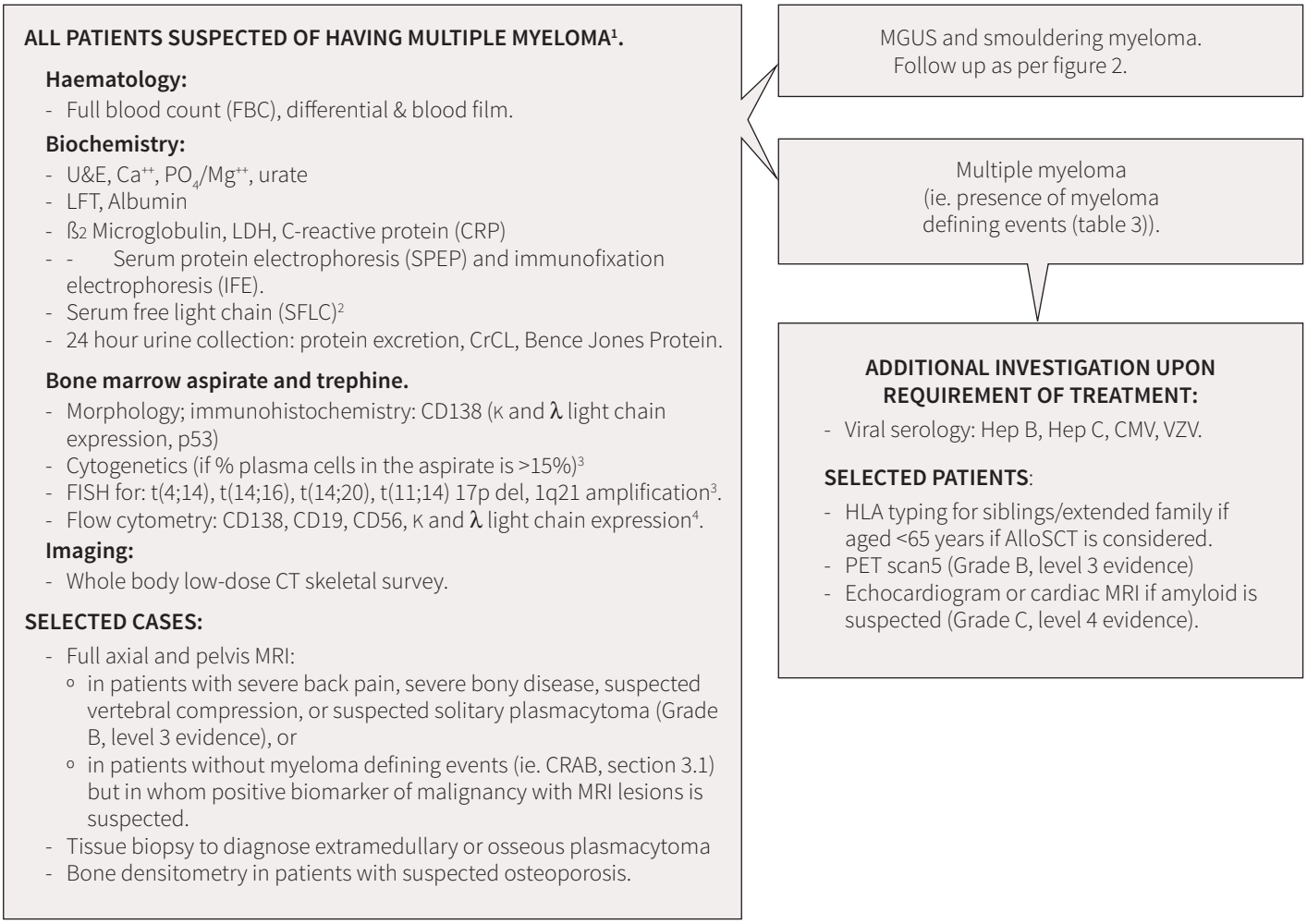
1 *t(4;14) and del(17p) are often associated with del(13q) and it appears that most of the negative impact of del(13q) is related to t(4;14) or del(17p).*

2 *Cytogenetics and FISH should only be requested in patients in whom the identification of high-risk would impact management. Cytogenetics is often only possible in patients with >15% plasma cells in the aspirate as the yield of metaphases is low with a lesser plasma cell burden.*

2.2 INVESTIGATION AT INITIAL DIAGNOSIS

The initial diagnostic work-up process (Figure 1) aims to establish the diagnosis, the stage of disease, and prognostic markers, which may influence subsequent treatment. The following recommendations are grade C and based on level 4-evidence unless otherwise stated

Figure 1: Initial diagnostic work up



1. The extent of initial diagnostic work up for patients with MGUS is more limited compared to patients suspected of having multiple myeloma, and is dependent on the level of paraprotein and individual risk assessment for progression towards multiple myeloma. Please refer to the recent international myeloma working group (IMWG) consensus [8]
2. The serum immunoglobulin-free light chain (SFLC) assay is recommended by the IMWG as part of screening in combination with SPE and IF, which altogether yields high sensitivity, and may be used in place of 24 hour urine BJP [9].
3. Cytogenetics is often only possible in patients with >15% plasma cells in the aspirate as the yield of metaphases is low with a lesser plasma cell burden.
4. Additional markers for the standardised detection of minimal residual disease is as per the Euroflow-based next generation flow approach [10]
5. PET can be useful additional diagnostic tools for detection of otherwise occult myelomatous sites in early stage MM. Sensitivity of PET in detecting myelomatous involvement is ~85% and specificity is ~92% [11]. PET is more sensitive than conventional radiography in detecting osseous MM involvement. Compared to MRI, PET failed to show abnormal areas of bone marrow involvement in up to 30% of patients detected by MRI. However, PET can sometimes detect abnormalities, which are out of field of view of MRI. PET is most useful in monitoring disease response in patients with extramedullary or non-secretory MM. Please refer to the MSAG Clinical Practice Statement on Imaging of patients with MM and plasma cell disorders [https://myeloma.org.au/wp-content/uploads/2021/05/MSAG_Imaging-Guidelines_May-2021.pdf].

3 MANAGEMENT OF MULTIPLE MYELOMA – AN OVERVIEW

Between 2012 to 2018, patients with MM in Australia had a median OS of 5 years according to data from the Australian Myeloma and Related Diseases Registry (MRDR; www.mrdr.net.au), but this is anticipated to improve with better standards of care and expanding treatment options. The expansion of effective treatments has converted what was once a disease with median overall survival (OS) of 3 years, to now a chronic disease capable of long-term control, often for 7 years or more. While we continue to strive towards to ultimate goal of "cure" for the future, currently, the treatment goals in the management of MM are to control the disease, maximise quality of life and prolong survival.

3.1 THE DECISION TO COMMENCE MYELOMA THERAPY

A key step in managing MM is to determine which patients require therapy, and the following applies to both transplant-eligible (TE) and transplant-ineligible (TIE) patients. This decision is generally determined by the presence of myeloma defining events, manifested by either hypercalcemia, renal impairment, anaemia or bone disease (so-called CRAB criteria) or positive biomarkers of malignancy (so-called SLiM-CRAB criteria; table 3) that predicts an 80% chance/risk of developing end organ damage within 2 years [2]

The average risk of progression from monoclonal gammopathy of uncertain significance (MGUS) to symptomatic myeloma is approximately 1% per year[17]. For SMM, the median time to progression is between 12 to 32 months[4]. Monitoring of MGUS and SMM should be indefinite; the frequency may vary depending on the individual's risk of progression.

High Risk Smouldering Myeloma

Early intervention in patients with MGUS and SMM is of no proven clinical benefit. However, the role of early treatment in the subset of patients with "high-risk" smouldering myeloma (HR-SMM) is still being evaluated. Complicating interpretation of studies of HR-SMM is the lack of a unified definition of this condition, with only a 30% concordance rate between the Mayo clinic and Spanish models [18].

There are two schools of thought with respect to proposed future management of HR-SMM. The first is that of an aggressive approach akin to that for active MM, with the ambitious aim to cure, given that myeloma cell clones may be more amenable to complete eradication at this stage. The second is that of a gentler approach with the aim of delaying progression and perhaps improve OS. The initial phase III QuiRedex study that showed improved OS with Rd compared to placebo for high-risk SMM is no longer interpretable in the context of SMM, as a proportion of the so called high-risk SMM in that study would be considered to have MM, based on the SLiM CRAB criteria [19]. Following that study, the Spanish GEM-CESAR study adopted an aggressive approach for patients with HRMM (excluding patients with SLiM CRAB criteria), with 6 cycles of induction KRd (carfilzomib, lenalidomide and dexamethasone) followed by MEL200 ASCT, 2 cycles of KRd consolidation, then Rd maintenance), and reported ORR 100% with CR 75% and MRD negativity of 60%. This high rate of response should be weighed up with the potential morbidity and spectrum of long-term consequences of ASCT in what is smouldering disease. Meanwhile, the phase III E3A06 study of lenalidomide versus placebo for patients with HR – SMM as defined by the Mayo 2008 and 2018 (2/20/20) model, reported improved PFS for patients in the lenalidomide arm (HR 0.28, p=0.002) at median follow up of 35 months, with yet no difference in OS[20].

Box 1: Recommendation for monitoring of MGUS and Asymptomatic MM:

Monitoring of MGUS and asymptomatic MM should be indefinite; the frequency may vary depending on the individual's risk of progression (Grade C recommendation).

Three to 12 monthly visits are sufficient, depending on the individual risk assessment for progression towards symptomatic MM. (Grade C recommendation).

Monitoring should include a clinical assessment, full blood evaluation, renal function, electrolytes including calcium levels, serum ± urinary paraprotein, and targeted radiographic imaging when indicated. (Grade C recommendation).

Early treatment of patients with "high-risk" multiple myeloma (as defined by either the Spanish or Mayo criteria, see text) is still considered investigational and should be only undertaken in a clinical trial setting.

Patients without evidence of myeloma defining events (CRAB criteria, table 3) but with positive markers of malignancy (SLiM CRAB criteria) (table 3) are now classified as having multiple myeloma and should be treated as such.

This paved the way for the ongoing phase III ITHACA study of isatuximab-lenalidomide versus lenalidomide monotherapy for patients with HR-SMM (clinicaltrials.gov **NCT04270409**). Similarly, the phase II CENTAURUS study[21] of daratumumab (in three different schedules) for patients with HR-SMM reported a favourable safety profile and efficacy (ORR up to 56%) and led way to an ongoing phase III AQUILA study of daratumumab monotherapy versus placebo in patients with HR SMM (clinicaltrials.gov **NCT03301220).**

While confirmatory studies are awaited, commencing anti-myeloma treatment for patients with HR-SMM should be part of clinical trials. Therapies for HR-SMM is not TGA approved nor reimbursed in Australia. Figure 2 and Box 1 outlines the recommended follow up algorithm for patients with MGUS and SMM and HR-SMM.

3.2 UPFRONT TREATMENT OF MULTIPLE MYELOMA – AN OVERVIEW

Initial treatment for patients with newly diagnosed MM (NDMM) depends on their eligibility for high dose therapy (HDT) and autologous stem cell transplant (ASCT), that is in turn dependent on the patient's age, comorbidities and functional status. Whether or not ASCT is incorporated as part of initial treatment, the aim is to induce a maximal depth of response, ideally complete response (CR) or better, without unacceptable toxicities. CR or better is associated with prolongation of PFS and OS [22, 23]in both the ASCT[24-26] and non-ASCT setting[23, 27, 28], and in both young and elderly patients. However, the prognostic impact of CRs on survival may be less important in patients in whom symptomatic myeloma had progressed from a previous prolonged period of MGUS or smouldering myeloma[29]. Conversely, the prognostic impact of achieving CR or better on survival is more evident in patients with high-risk versus standard risk MM as defined by gene-expression profiling[30]. Currently, achieving CR or better is considered an objective of initial treatment, provided there is no unacceptable toxicity. Amongst patients with CR, MRD (minimal residual disease) negativity as defined by multi-parameter flow cytometry, polymerase chain reaction or next generation sequencing, has been shown to correlate strongly with OS. MRD negativity is increasingly accepted as a surrogate correlate for improved OS[31]. At present, methods for assessment of MRD are not consistent across laboratories and generally only available in tertiary treatment centres in Australia. MRD is not generally used to influence treatment decisions and is therefore mainly used in the clinical trial setting.

3.2.1 Patients eligible for ASCT

The superiority of ASCT (when used as part of initial therapy) over a non-transplant approach has now been confirmed in the era of IMiDs and proteasome inhibitors in four randomised phase III trials. In both the GIMEMA MM-RV-209[32] and EMN MM-RV-441 trial, patients aged <65 years were given lenalidomide-dexamethasone induction prior to stem cell collection, then randomised to either ASCT or a further 6 cycles of MPL (Melphalan, Prednisone, Lenalidomide; GIMEMA trial) or RCd (lenalidomide, cyclophosphamide, dexamethasone; EMN trial). Both studies have demonstrated superiority of the ASCT approach as part of initial treatment with respect to PFS and OS. Similar results were seen in the phase III IFM 2009 study evaluating bortezomib lenalidomide dexamethasone (VRd) induction with or without upfront ASCT, then lenalidomide maintenance. Marked improvement in PFS was seen with the upfront ASCT approach (HR 0.69, p<0.001) [33]. Importantly, an impressive superiority in the rate of MRD negativity was seen with the ASCT approach (80% (ASCT arm) vs. 65%, p 0.001), which in turn is generally correlated with improved OS[31]. Finally, in the EMN02/HO95 study, incorporating ASCT as part of initial treatment was superior to ongoing VMP (bortezomib, melphalan, and prednisone) with respect to PFS[34]. Meta-analysis of the major studies indeed confirmed superior PFS by incorporating ASCT to initial treatment[35]. However, longer-term follow up is required to delineate any OS benefit, which will also be affected by subsequent therapies.

The traditional notion that patients aged above 65 years are ineligible for ASCT is no longer appropriate as it is clear that older patients who are biologically fit do benefit from intensive treatment[36]. In assessing eligibility for ASCT (generally in patients aged up to 70 years), individual assessment that takes into consideration the patient's age, comorbidities, frailty (variously defined as poor endurance, weakness and low physical activity) and disability (dependency in activities of daily living (ADL) due to physical or mental impairment)[37] is required (please refer to the section on patients ineligible for ASCT). Clinical tools such as the haematopoietic stem cell transplant co-morbidity index (HCT-CI) may be useful to assess suitability for ASCT[38].

3.2.1.1 Tandem vs. Single ASCT

Prior to the era of IMiDs, PIs, and other novel therapeutic agents, tandem ASCT (in which the second ASCT is planned to occur 3 to 6 months after the first) was found to benefit mainly patients who have not achieved at least VGPR to the initial transplant[39, 40]. The role of routine tandem ASCT in the era of effective induction (IMIDs and/or PI) and effective maintenance remains a matter of debate, but there is a stronger rationale for patients with high-risk disease.

In a meta-analysis of 6 randomised-control trials of 1803 patients, comparing tandem versus single ASCT for upfront treatment of MM, Kumar et al[41] reported that whilst there was a superior overall response rate (ORR) with tandem ASCT (risk ratio 0.79), there was a significant increase in transplant related mortality (TRM) (risk ratio 1.71). Overall, tandem ASCT did not result in improved OS or EFS compared to

single ASCT. However, the trials that were included in this meta-analysis were heterogeneous, mainly due to the inclusion of a trial that was not designed to compare single versus double ASCT, but rather single transplant plus thalidomide maintenance therapy versus tandem transplant, ie. thalidomide maintenance post single ASCT improved PFS thus confounded the result [42]. Indeed, when that study was retracted from the meta-analysis, tandem transplant resulted in improved EFS, but not OS.

In a more recent long-term follow up (median 117 months) analysis of data combined from three European phase 3 studies (GIMEMA MMY -3006, PETHEMA/GEM and HONVON65MM/GMMG-HD41), tandem ASCT resulted in superior PFS (HR 0.76 (p=0.001) and OS (HR 0.69 (p<0.001) compared with single ASCT. Subgroup analysis demonstrated superiority in the tandem ASCT arm particularly in patients with high-risk cytogenetics, higher ISS stage and in patients who have not achieved CR , but not in patients with low-risk disease (ISS 1)[43].

Conversely, in the primary analysis of the StaMINA trial, tandem ASCT had no impact on PFS and OS compared to single ASCT when effective induction (combination IMID and PI) and lenalidomide maintenance was incorporated (see section on consolidation)[44]. One criticism of the StaMINA study however, is that patients were allowed to receive more than 4 (up to 12) cycles of induction therapy prior to randomisation to second ASCT/other consolidation, which, may have had an additive consolidative effect prior to randomisation to consolidation. In a long term follow-up[45], there was a suggested benefit of tandem transplant, mainly in patient with high-risk MM.

At present, tandem ASCT with its associated acute toxicity may be a reasonable strategy in selected patients who have had a suboptimal response to first transplant, and in particular patients with high-risk MM[46]. Otherwise, consolidation or maintenance therapies with newer agents, and effective salvage therapies in the current era, may well mitigate any OS advantage of tandem ASCT over single ASCT. Our recommendations for transplant eligible patients is as outlined in Box 2.

Box 2: Recommendation regarding autologous stem cell transplant (ASCT)

High dose therapy (HDT) and autologous stem cell transplant (ASCT) remains the standard upfront treatment for patients aged ≤65 years, and patients between 65-70 years with good performance status and organ reserve (Grade A recommendation, level 1A evidence for patients age ≤65; grade B recommendation, level 2A evidence for patients aged >65)

Tandem ASCT may be considered particularly in patients with high-risk cytogenetics, who have not achieved CR after the first ASCT, and provided that the patient has achieved at least a PR and without unacceptable toxicity to the first ASCT. (Grade A recommendation, level 1B evidence).

3.2.1.2 Induction therapy prior to ASCT

The ideal induction regimen for transplant-eligible patients should rapidly reduce tumour burden and reverse disease related complications, to allow patients to proceed promptly to transplant without antecedent toxicities. Deeper pre-transplant response is associated with better post-transplant outcome[47]. Induction-regimens that incorporate IMiDs and /or proteasome inhibitors (table 7A) are superior to chemotherapy-only regimens, particularly in poor-risk patients such as those with poor cytogenetics or other adverse prognostic features[48-50].

As of the 1st of June 2020, the combination of bortezomib, lenalidomide and dexamethasone (VRd) for the upfront treatment of patients with MM was made available on the Australian Pharmaceutical Benefits Scheme. The two major phase III studies that incorporated VRd as induction therapy prior to ASCT were the IFM 2009 and the PETHEMA study with slightly different VRd schedules. In the **IFM2009 study**, VRd regimen was given in a 21-day cycle and comprised: bortezomib 1.3mg/m2 IV on days 1,4,8,11, lenalidomide 25mg po on days 1-14 and dexamethasone 20mg on days of and days after bortezomib. Stem cell mobilisation was performed after 3 cycles of VRd using high-dose cyclophosphamide (3g/m2) for mobilisation prior to ASCT, followed by 2 further cycles of consolidation VRd before lenalidomide maintenance. ORR post ASCT was 99% with a CR rate of 59% and 4 year PFS 47m. In the **PETHEMA study**, VRd schedule was given over a 28-day cycle with bortezomib on days 1,4,8,11, lenalidomide 25mg days 1-21 and dexamethasone in pulses of 40mg days 1-4, 9-12. Here stem cells were collected after 3 cycles. Post ASCT, ORR was 81% with CR rate of 44% and an MRD negativity (10-6) of 28.7%.

Peripheral neuropathy was not an uncommon issue with both the IFM2009 and PETHEMA schedules of VRD; grade≥3 peripheral neuropathy occurred in 12.9% of patients in the 21-day schedule (IFM-2009) and 3.9% in the 28-day schedule (PETHEMA).

To improve tolerability, two groups explored different versions of dose attenuated VRd, so called VRd-Lite[51, 52]. The **Japanese study** tested VRd-Lite in an approach that incorporated upfront ASCT [51]. Here, four 28-day cycles of weekly bortezomib (1.3mg/m2 sc D 1,8,15,22) in combination with lenalidomide 25mg orally days 1-21 except on the days of bortezomib and dexamethasone 40mg weekly was given

prior to ASCT. ORR was 83% (≥VGPR 48%) after 4 cycles prior to ASCT. Importantly, grade ≥3 peripheral neuropathy was only 3%. Similarly, **Mookerjee** et al.[53] reported a phase III study (abstract publication) of 143 patients, comparing two VRd-lite schedules in cycles of 28 days: Arm A (Bortezomib 1.3 mg/m2 sc on days 1, 8, 15 and 22 with lenalidomide 15mg po days 1-14) and Arm B (Bortezomib 1.3 mg/m2 sc on days 1, 8, 15 and 22 with lenalidomide 25mg po days 1-21). Patients only received 4 cycles of treatment, which induced similar ORR and depth of response between arm A and B (ORR/CR rates 78%/28% and 74%/30%, respectively.)

For the treatment of transplant eligible patients, the MSAG recommend the following:

- ASCT as part of initial treatment remains the standard of care.
- As the current PBS reimbursement of VRd for TE patients is based on the SWOG SO777 study in which ASCT was not incorporated upfront, the number of funded-bortezomib doses (total 32) is more than what is utilised in any of the aforementioned studies that incorporate upfront ASCT. Drawing from the analogy that that a higher cumulative dose of bortezomib correlates with improved OS in transplant ineligible patients, it is not unreasonable for clinicians to adapt a VRd schedule with upfront ASCT in such a way so as to maximise the use of what is offered on PBS to optimise patients' outcome, provided that there is no unacceptable treatment emergent toxicity. That is, to utilise the remaining doses of bortezomib (with or without lenalidomide) in *consolidation* post ASCT either in a weekly[54] or every two weekly[55] schedule to further deepen response prior to embarking on maintenance lenalidomide monotherapy.
- Subcutaneous route of bortezomib administration is preferred to intravenous to minimise peripheral neuropathy. Past studies have shown that a weekly schedule of bortezomib appears to result in reduced toxicity without compromising efficacy compared to the traditional schedule of bortezomib 1.3mg/m2 days 1,4,8,11 every 21 days[56].
- Weekly *subcutaneous* bortezomib is better tolerated than intravenous (IV) without compromising efficacy in transplant eligible patients [57]. If a twice-weekly bortezomib schedule is used per the IFM 2009 or PETHEMA studies, vigilance is required for the development of peripheral neuropathy that may occur precipitously post ASCT. Prompt withhold of bortezomib and/or dose reduction is required in the event of grade 3 (CTCAE) peripheral neuropathy particularly upon burning/painful symptoms to avoid irreversibility. Alternatively, a weekly schedule of bortezomib may be adopted at the outset.

In patients who are unable to receive lenalidomide due to severe renal impairment, three-drug induction that incorporate bortezomib, dexamethasone and a chemotherapy (cyclophosphamide [VCd])[56, 58] or the first generation IMiD, thalidomide (VTd) [59] are also accepted standard of care for induction prior to ASCT. Of note, thalidomide is not PBS-reimbursed when used in combination with bortezomib but can be accessed privately at a modest cost.

With respect to quadruplet combinations for induction therapy, no further advantage was seen with a four-drug combination of IMIDs, PI, cyclophosphamide and dexamethasone, which instead results in greater toxicity[60]. In contrast, a four-drug combination that incorporates the anti-CD38 monoclonal antibody (mAb) Daratumumab with VTd (DVTd), VRd (Dara-VRd) or with KRd (carfilzomib, lenalidomde and dexamethasone; Dara-KRdCA), appeared well tolerated and highly efficacious[61]. In the CASSIOPEIA study [62], DVTd was superior to VTd, inducing an ORR of 92.6%, ≥CR of 39% and MRD negative -CR of 34%. PFS was superior for Dara-VTd compared to VTd; 18 months PFS was 92% vs. 85%, respectively, HR 0.47, p<0.0001. Dara-VRd was highly efficacious and superior to VRd in the phase II randomised GRIFFIN study[63], inducing a ORR of 100% post consolidation post ASCT (≥CR of 56% and MRD negative rate of 50%). These results await confirmation in the ongoing phase III randomised PERSEUS study of Dara-VRd vs. VRd as induction and consolidation post ASCT (ClinicalTrials.gov Identifier: NCT03710603). As of 2021, daratumumab is registered by the TGA for use in combination VTd for induction therapy in TE patients, but is not reimbursed by the PBS. Recommendation for initial therapy of TE patients are outlined in box 3.

Box 3: Recommendation for initial therapy for transplant eligible patients.

- The incorporation of ASCT upfront in the current era remains the standard of care (level 1A evidence, grade A recommendation).
- Triplet combination bortezomib lenalidomide and dexamethasone (table 7A) is reimbursed by the PBS and is considered the current standard of care for induction therapy prior to ASCT (level 1B evidence, grade A recommendation)
    - As the total PBS-reimbursed doses of bortezomib (total 32) is more than what is utilised in published studies that incorporate upfront ASCT, it is not unreasonable for clinicians to use the remaining doses post ASCT, to further deepen responses, provided that there is no unacceptable treatment emergent toxicity
    - Subcutaneous route of bortezomib administration is highly preferred to intravenous to minimise peripheral neuropathy. Intravenous route of administration should only be used if patients develop unacceptable skin reaction to subcutaneous bortezomib injections.
    - When a twice weekly bortezomib schedule is used, vigilance is required for the development of peripheral neuropathy.
    - A weekly schedule of bortezomib 1.3 mg/m^2 and subcutaneous route of administration appear to significantly reduce neurotoxicity compared to the traditional bortezomib schedule of 1.3mg/m^2 IV on days 1,4,8,11 every 21 days. The use of weekly bortezomib is acceptable to minimise the risk of peripheral neuropathy (level 2A evidence, grade B recommendation)
    - Lenalidomide is available on the PBS as either (i) 8 x 21 day cycles [14 days of lenalidomide] or (ii) 6 x 28 day cycles [21 days of lenalidomide]. Either dosing schedule is acceptable and expected to achieve equivalent results.
- In situations where either bortezomib or lenalidomide is contraindicated, for example, severe peripheral neuropathy or renal impairment, respectively, either can be replaced by cyclophosphamide for an alternative triplet induction regimen prior to ASCT (level 1B evidence, grade A recommendation), table 7A.
- Quadruplet combination of VRd plus cyclophosphamide is not routinely recommended (level 1B evidence, grade A recommendation)

Table 7A: Induction therapy for transplant-eligible patients.

REGIMEN	SCHEDULE	COMMENTS
VRd		
VRd IFM 2009[2] (phase III RCT)	**Induction**: 21-day VRd cycle: V 1.3mg/m^{2}IV D1,4,8,11 R 25mg po D1-14 d 20mg D1,2,4,5,8,9,11,12 Schedule: Three 21-dayVRd cycles thencyclophosphamide 3g/m^{2}stem cell mobilisation, then Mel200 ASCT then two 21-day VRd consolidation cycles then R maintenance. **R maintenance:** Twelve 28-day cycle. R 10mg (15mg if tolerated from cycle 4) po D1-28	Please see section 3.1.2.1 for detailed discussion. - Subcutaneous bortezomib preferential to IV administration to minimise peripheral neuropathy - Vigilance is required for the development of peripheral neuropathy. Prompt withholding of bortezomib and/or dose reduction is required in the event of grade 3 (CTCAE) peripheral neuropathy particularly with burning/painf to avoid irreversibility. Alternatively, a weekly schedule of subcutaneous bortezomib may be adopted at the outset as it is better tolerated and isunlikely to compromise efficacy [57, 93].
VRd PETHEMA[12] (phase III RCT)	**Induction:** 28-day VRd cycle: V 1.3mg/m^{2}IV D1,4,8,11 R 25mg po D1-21 d 40mg days 1-4, 9-12. Schedule Three 28-dayVRd cycles then stem cell mobilisation (mode not specified) and ASCT, then2 VRd consolidation cycles the Rmaintenance. **R maintenance:** Twelve 28-day cycle. R 10mg (15mg if tolerated from cycle 4) po D1-28	
VRd-Lite		
VRd-Lite[3]	**Induction:** 28-day VRd cycles: Bor 1.3mg/m^{2}sc D 1,8,15,22 Len 15mg po D1-21 (omit on days of Bor) Dex 40mg D1,8,15,22 **Schedule:** Four 28-day cycles of VRd then GCSF + plerixafor or cyclophosphamide stem cell mobilisation then MEL200 ASCT.	Note that this is a phase II single arm study of only 48 patients.

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REGIMEN	SCHEDULE	COMMENTS
VTd		
VTd[59, 62]	**Induction therapy:** V 1.3mg/m^2 IV D1,4,8,11 T 100mg po daily D 40mg po on day of and day after V for cycles 1 and 2; for cycles 3 and 4, 40mg on days 1,2 and 20mg days 8,9, 15,16; for cycles 5 and 6, 20mg on days 1,2,8,9,15,16) Schedule: Four 28-day cycles of VTd stem cell mobilisation and MEL200 ASCT, then 2 cycles of VTd consolidation prior to maintenance.	Comments from MSAG: The addition of Daratumumab to VTd (DaraVTd) is superior to VTd with 53% reduction in progression or death (p<0.0001). As of 2021, daratumumab is registered by the TGA for use in combination VTd for induction therapy in TE patients, but is not reimbursed by the PBS VTd is an option when VRd is not feasible due to contraindications to lenalidomide (eg severe renal failure). - Subcutaneous bortezomib preferential to IV r administration to minimise peripheral neuropathy. Prompt withholding of bortezomib and/or dose reduction is required in the event of grade 3 (CTCAE) peripheral neuropathy particularly if there isburning/ pain to avoid irreversibility. Alternatively, a weekly schedule of bortezomib (sc) may be adopted at the outset as weekly subcutaneous bortezomib is better tolerated than intravenous (IV) without compromising efficacy even in transplant eligible patients [57].
VCd		
CyBorD/VCd [56, 161, 162]	**Induction:** V 1.3mg/m^2 IV D1,4,8,11 C 300mg/m^2 po D1,8,15 d 20mg po on day of and day after bortezomib. Schedule: Cycles repeated every 21 days x for 3-4 cycles prior to ASCT **OR** V 1.5mg/m^2 sc D1,8,15,22 C 300mg/m^2 po D1,8,15,22 D 20mg po on day of and day after bortezomib. Schedule: Cycles repeated every 28 days x for 3-4 cycles prior to ASCT	MSAG comments: VCd is an acceptable option when VRd is not feasible due to contraindications to lenalidomide or severe renal failure.

RCT: randomised controlled trial; V: bortezomib; R: lenalidomide; d: dexamethasone; T: thalidomide; Mel: melphalan; dara: daratumumab; IV: intravenous; po: oral; sc: subcutaneous

3.2.1.3 Stem cell mobilisation

The most common regimens used to mobilise peripheral blood stem cells (PBSC) for MM patients is recombinant human granulocyte colony stimulating factor (rhG-CSF), such as filgrastim™, 10mcg/kg, or high dose cyclophosphamide with rhG-CSF. The addition of high dose cyclophosphamide for mobilisation does not necessarily improve depth of response over induction therapy and does not improve CR rates or time to progression (TTP) in patients undergoing ASCT[64]. However, using cyclophosphamide for mobilisation has the advantage of increasing the CD34+ cell yield. A higher dose of cyclophosphamide (3-4g/m^2) will give a better CD34+ yield, but may also cause more toxicity requiring hospital admissions compared to cylophosphamide 2g/m^2[65], with a potential negative effect on OS and lymphocyte recovery{Rees, 2021 #2667}.

Plerixafor (Mozobil®), a chemokine receptor-4 antagonist, has been shown to be a potent stem cell mobiliser. Its use in combination with rhG-CSF significantly improves stem cell mobilisation compared to rhG-CSF alone[66]. Due to high cost, plerixafor is generally reserved for patients who fail to mobilise adequately as either a rescue strategy or during a second mobilisation attempt, under the PBS re-imbursement criteria in Australia (pbs.gov.au).

Bortezomib and thalidomide does not appear to impair stem cell mobilisation [67] in patients who have received fewer than 4 induction treatment-cycles. In these cases, rhG-CSF alone is often adequate for the initial attempt at stem cell mobillisation although many centres continue to use rhG-CSF in addition to high-dose cyclophosphamide as part of institutional protocol. Of note, recent reports have indicated that thalidomide and oral cyclophosphamide, two agents that have not been shown to impact stem cell mobilisation individually, may induce a higher rate of stem cell mobilisation failure when used in combination[68]. Lenalidomide is known to negatively impact stem cell mobilisation. Stem cell collections post VRd induction in the IFM2009 and PETHEMA studies were performed usually after 3 to 4 cycles of VRd, with G-CSF (granulocyte-colony stimulating factor) and either high dose cyclophosphamide[33] or plerixafor[51]. Australian data have shown successes with 'double dose' G-CSF alone when stem cell collections are performed earlier, after 3 cycles of VRd , however, further studies are required.

Recommendations for stem cell mobilisation are summarised in box 4.

Box 4: Recommendation for stem cell mobilisation:

- *Stem cell mobilisation regimen should follow institution protocol.*
- *Stem cells can be mobilised with rhG-CSF alone or rhG-CSF(10mcg/kg) in combination with high-dose cyclophosphamide (2 to 4g/m2) or plerixafor.*
- *The use of high-dose cyclophosphamide has the advantage of increasing CD34+ yield, but is also associated with more toxicity.*
- *Plerixafor in combination with rhG-CSF significantly improves stem cell mobilisation and is reserved for patients who fail to mobilise adequately on cyclophosphamide plus rh-GCSF, or rhG-CSF alone (Grade B recommendation, level 2B evidence).*
- *As lenalidomide is known to negatively impact on stem cell yield, suggest early stem cell collection after cycles of VRd.*
- *Australian data have shown successes with 'double dose' rhG-CSF alone when stem cell collections are performed earlier, 3 cycles of VRd. However, rhGCSF plus cyclophosphamide or plerixafor may be required for stem cell mobilisation. (Grade B recommendation, level 2B evidence).*

3.2.1.4 Monitoring of patients after ASCT

The average time to progression for patients after HDT and ASCT is in the order of 2-4 years for younger patients, and shorter for older patients. The final magnitude of response post ASCT should be assessed after 2-3 months. Patients should be followed up with clinical and laboratory assessments, looking for evidence of relapse/progression. Testing should include serum or urinary paraprotein and SFLC levels (especially in patients with non-measureable paraprotein in blood or urine), FBC, serum calcium levels, and renal function. In assessing response, it is important not to misinterpret the emergence of oligoclonal bands as relapse disease or clonal evolution. Oligoclonal response after primary therapy is a well-recognised event, and can appear as multiple oligoclonal bands in serum and/or urine immunofixation; it is thought to be related to immune reconstitution and is associated with favourable outcome[69]. Initial follow up for patients is usually monthly until stable, then 3 monthly or less frequent subsequently if there appears to be disease stability. Recommendation regarding follow up post ASCT are summarised in box 5.

Box 5: Recommendations regarding follow up post ASCT:

- *Post HDT+ASCT, patients should be followed up monthly until stable, then 3 monthly or less frequent if there appears to be disease stability (grade C recommendation, level 4 evidence)*
- *Follow up assessment should include:*
  - *Clinical assessment.*
  - *Serum ± urinary protein electrophoresis (immunofixation not required)*
  - *Serum free light chains.*
  - *FBE, U&E, Ca^{2+}*
  - *Targeted radiographic imaging if indicated.*

3.2.1.5 Allogeneic Stem Cell Transplant

"Graft versus myeloma (GVM)" effect does exist in the setting of allogeneic stem cell transplantation (alloSCT) [70]. However, while this may give rise to some long-term durable remissions [71], myeloablative alloSCT is associated with a high TRM of up to 50%. Reduced intensity conditioning (RIC) alloSCT lowers TRM to approximately 10-15% at 1 year, whilst maintaining the GVM effect, however chronic graft-versus-host disease remains a major problem in many survivors. A number of prospective trials have been published. The IFM99-03 study [72], included only patients with high-risk (del13q + B_2M>3mg/ml), and patients with available sibling donors underwent MEL200 ASCT followed by RIC AlloSCT with anti-thymocyte globulin, busulphan and fludarabine conditioning. Patients without a donor had a second ASCT in the companion IFM99-04 study. At the time of initial reporting median EFS and OS were similar in the two studies, EFS 35 months vs 32 months, p=ns, and OS 47 months vs 35 months, p=ns, in ASCT + RIC alloSCT vs. tandem ASCT respectively. However after longer follow up, OS was found to be significantly inferior in patients assigned to RIC alloSCT [73]. An Italian randomised study, also comparing tandem ASCT vs. ASCT followed by RIC alloSCT (non-myeloablative total body irradiation conditioning), and not requiring poor prognostic features for selection demonstrated a superior long-term outcome in those who had available sibling donors (OS: 80 vs. 54 months, p=0.01; EFS: 35 vs.29 months. P=0.02) [74]. In the Spanish PETHEMA trial [75], comparisons were made between a second ASCT vs. RIC (melphalan and fludarabine) alloSCT in a group of patients who achieved < VGPR to their first ASCT. A higher rate of CR in favour of RIC alloSCT was seen (40% vs. 11%, p=0.001) and a plateau in PFS was also seen in this group. However, due to a higher TRM and GVHD, no statistical difference in EFS and OS was observed. Similarly, interim results from the BMT-CTN (Blood and Marrow Transplant Clinical Trials Network) 0102 Trial showed equivalent 3-year PFS and OS for tandem auto-auto vs. auto-allo stem cell transplant both high-risk [76], and standard-risk [77] MM patients. Two Gy total body irradiation was used as the non-myeloablative conditioning regimen in the allo-SCT arm. There was a suggestion of lower late PFS and time to progression/relapse in the auto-allo SCT arm in the high-risk group (p=0.09), however, no added benefit from auto-allo SCT was seen in the standard-risk group over tandem ASCT due to increased TRM. At present, a number of studies are ongoing to investigate the role of AlloSCT with novel immunological approaches. However, given the lack of consistent survival benefit to date, the use of AlloSCT should still be restricted to clinical trials, with the exception of selected cases of very high-risk MM (please see section 3.4: patients with high-risk MM)[78]. Recommendations regarding AlloSCT are summarised in box 6.

Box 6: Recommendation regarding AlloSCT:

- *Currently, alloSCT is still considered investigational and should ideally be performed in the setting of a clinical trial (Grade C recommendation).*
- *Young patients with very high-risk disease (please refer to section 3.4) who are deemed suitable for AlloSCT should be referred early to the transplant physician at the outset of treatment (Grade C recommendation).*

3.2.2 Patients not eligible for ASCT

3.2.2.1 Pre-treatment consideration: fit versus frail elderly patients

Aging is associated with comorbidities and reduced organ function that may reduce tolerance to therapy. Whilst the goal of achieving complete remission (CR) is important irrespective of age[79], substantial treatment-related toxicities can mitigate benefits of CR in frail elderly patients. In the group of frail elderly patients, opting for disease control to optimise quality of life (QoL) may be preferable.

For elderly patients, minimization of treatment related toxicities will improve duration on treatment and correlate with improved survival [80]. As such, robust **frailty assessment** is required for choosing the appropriate induction regimen. The International Myeloma Working Group (IMWG) frailty score[81] is widely accepted. Based on age, comorbidities, frailty (variably defined as poor endurance, weakness and low physical activity) and disability (dependency in activities of daily living (ADL) due to physical or mental impairment), elderly patients can be divided according to three broad subgroups: fit, intermediate fit and frail. Broadly speaking, fit patients are patients with excellent performance status, no significant co-morbidities (in particular cardiac, pulmonary, renal, hepatic or gastrointestinal), disabilities or frailty. Intermediate-fit patients are patients with comorbidities or factors that may preclude ASCT, but have reasonable performance status and no significant disabilities. Frail patients are those of older age (typically but not always, patients aged above 80 years) with significant co-morbidities, limitations in physical activity and/or dependency in ADLs due to physical or cognitive impairment[82].

The traditional notion that patients aged above 65 years are ineligible for transplant is no longer appropriate. For patients aged between 65-70 who are fit, induction therapy incorporating IMiDs or proteasome inhibitors followed by HDT+ASCT and subsequent maintenance can induce profoundly deep responses[83, 84] (Please refer to section on transplant eligible patients). Reduced-dose conditioning (melphalan 100-140mg/m^2)[83, 84] is tolerable and has been shown to induce a median PFS of 4 years in this group of patients[83].

Patients who are otherwise ineligible for ASCT but who are fit or Intermediate-fit should undergo standard treatment regimens containing an IMiD and/or a proteasome inhibitor, while frail patients should be considered for doublet therapies with or without reduced dose-intensity (please see box 7).

Box 7: Recommendations for the assessment of suitability of elderly patients for the intensity of therapy:

- *Frailty assessment is required to guide treatment choice.*
- *Fit patients aged between 65-70 can be considered for full dose induction therapy incorporating IMiDs and proteasome inhibitors followed by HDT+AuSCT. For VRd induction, weekly subcutaneous use of bortezomib in a 28-cycle may be considered instead of twice-weekly bortezomib schedule to reduce the risk of peripheral neuropathy. Reduced dose conditioning (melphalan 100-140mg/m2) can be considered (Grade B recommendation, level 2A evidence)*
- *Patients who are deemed ineligible for HDT+AuSCT but are fit or intermediate-fit should undergo induction therapy incorporating IMiDs and/or proteasome inhibitors (see section 3.2.2.2; table 7B) (Grade A recommendation, Level 1A evidence)*
- *For frail elderly patients, doublet therapy or reduced-intensity triplet therapy is suggested (see table 9) (Grade B recommendation, Level 2A evidence)*
- *Patients who are considered ineligible for any treatment should be referred early to a palliative care unit.*

3.2.2.2 Initial treatment for transplant ineligible (TIE) patients

Maximising the effectiveness of first-line therapy remains the best opportunity to optimise long term patient outcomes. Thus, three-drug combination, where feasible is preferred to achieve the best response rate and consequently a long first remission. However, for the older patients, the disadvantage of combining three drugs is the potential for more side effects. Our challenge is to balance tolerance with efficacy. It is recognised that the likelihood of drug-toxicity will be dependent on the patient's pre-treatment frailty. The challenge for clinicians is to assess frailty accurately.

Selecting patients for the 'right treatment' must go beyond just examining the characteristics of those entered on clinical trials. It is well recognized that although trial data is crucial for determining the efficacy of various therapies, the patients that enter such clinical trials do not always represent 'real world' patients and 'real world' outcomes. Indeed, in myeloma trials, the median age and performance status of patients on trials is typically lower than in the 'real world'[85].

Triplet combinations

Triplet combinations that are reimbursed on the PBS for induction therapy for TIE patients in Australia include combination IMID + PI + dexamethasone, VRd (bortezomib, lenalidomide and dexamethasone), combination PI + chemotherapy + corticosteroids (VCd: bortezomib cyclophosphamide dexamethasone; VMP: bortezomib, melphalan, prednisolone; PAD: bortezomib, anthracycline, dexamethasone)

The PBS reimbursement of VRd for induction therapy in TIE patents was based on the positive outcome of the SWOG S0777 study[86]. The initial report was updated in 2020 [87]. Importantly, this study enrolled patients *not specifically planned for front-line ASCT;* at a median follow up of 84 months, VRd was superior to Rd with respect to PFS (41m vs. 29m, HR 0.742, p=0.003) and OS (NR vs. 69m, HR 0.709, p = 0.0114). On subset analysis, the OS benefit of VRd was only significantly for those age <65. This was not surprising given that the patient population in this study was mainly transplant-eligible. In fact, 69% of patients had intent for upfront transplant and only 43% (38% in the VRd arm) of patients were age 65 years or older. Data was lacking regarding the clinical outcome and treatment emergent adverse events (TEAE) of the elderly group of patients over the age of 75 – who are generally considered transplant ineligible based on Australian practice.

There is no doubt that VRd is highly efficacious for TIE patients, however, for elderly patients, treatment related toxicities and early treatment cessation is a concern with the twice-weekly schedule of bortezomib as used in SWOG S0777, as these independently correlate with increased mortality [80].

Thus, when a lenalidomide-based regimen is considered for elderly TIE patients, considerations ought to be between a dose attenuated version of VRd, so called "VRd-lite" or lenalidomide-dexamethasone (Rd) doublet therapy. In one study **O'Donnell et al.**[52] explored VRd-lite for 50 TIE patents with a median age of 73 years (65-92). Here, VRd-lite consisted of nine 35 day cycles of induction bortezomib 1.3mg/m^2 subcutaneously on days 1,8,15,22 with low-dose lenalidomide 15mg po days 1-21 and dexamethasone 20mg on the days of and after bortezomib, followed by six 28-day cycles of consolidation consisting of bortezomib 1.3mg/m^2 every 2 weeks and lenalidomide 15mg days 1-21 without dexamethasone. After a median follow up of 30 months, best ORR was 86% with ≥VGPR 66% and median PFS was 35.1m. Grade 3 peripheral neuropathy only occurred in 1 patient.

The following is the view of members of the MSAG:

- If triplet VRd is chosen, the VRd-Lite regimen is deemed less toxic, noting that this has not been tested in phase III randomised studies against Rd
- Patients considered fit for the twice weeky bortezomib containing VRd schedule per the SWOG S0777 study, are likely to be able to tolerate upfront ASCT – clinicians are encouraged to consider this option. For frail patients, Rd remains an acceptable standard of care .
- Of note, in Australia, there are two national studies that are still accruing for initial treatment of transplant-ineligible patients which may provide further clarity on optimal induction for this group of patients:
  - The AmaRC 19-02/ALLG-MM22, FRAIL-M study (anzctr.org.au; ACTRN12619001199101) testing VRd-lite vs. Vd vs. Rd, and
  - The AmaRC 18-02, IRIL study (anzctr.org.au; ACTRN12619000362190) testing the addition of isatuximab to patients who have not achieved CR by 9 cycles of Rd (patients need to be enrolled prior to completion of cycle 4 of Rd).

For patients who are unable to receive lenalidomide (eg. severe renal impairment), bortezomib-based triplet induction of VCd or VMP are acceptable based on the VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma) study that showed superiority of VMP over MP (melphalan and prednisolone) with respect to PFS and OS [88]. Combination bortezomib, thalidomide and dexamethasone (VTd) does not appear superior for TIE patient compared to a simple (and cheaper) bortezomib and alkylkating agent with corticosteroids, but is particularly toxic with respect to cardiac adverse events[89, 90]. VTd is not reimbursed by the Australian PBS.

Of note, weekly schedule of bortezomib has been shown to be more tolerable and resulted in a similar cumulative dose delivered compared to the traditional schedule of bortezomib on days 1,4,8,11 every 21 days[91]. For TIE patients, the weekly schedule of bortezomib is now considered standard of care (table 7B). Subcutaneous bortezomib is non-inferior to IV bortezomib with respect to efficacy but has an improved safety profile[92]. IV Bortezomib is not recommended. The use of cyclophosphamide in place of melphalan is of comparable efficacy[56].

Thalidomide-based induction therapy are regarded as inferior to bortezomib or lenalidomide-based regimens and are not preferred unless there are contraindications to bortezomib and lenalidomide in the upfront treatment of MM. Thalidomide is often used in a triplet combination, with an alkylating agent (either cyclophosphamide [CTd] or melphalan [MPT]) and corticosteroid and comes at a price of higher toxicity, mainly, myelosupression, venous thromboembolism (VTE), and peripheral neuropathy for elderly patients. The use of cyclophosphamide as an alternative alkylating-agent to melphalan, in combination with thalidomide and dexamethasone (CTD) is equally efficacious as induction therapy[93](table 7B).

The addition of an anti-CD38 mAb to the current back-bones of induction for TIE patients is highly efficacious and well tolerated. Daratumumab in combination with the backbone of VMP (phase III randomised ALCYONE study)[94] or Rd (phase III randomised MAIA study)[95] significantly improved PFS, HR 0.5 for Dara-VMP vs. VMP, p<0.001 and HR 0.55 for Dara-Rd vs. Rd, p<0.0001, respectively. After long-term follow up of median 58 months, Dara-Rd resulted in improved OS compared to Rd (60-months OS 66.3% vs. 53.1%, HR 0.68, p=0.0013).In Australia, daratumumab is TGA registered for use in combination with either VMP or Rd for TIE patients with NDMM, but is not reimbursed by the PBS as of November 2021.

Doublet combinations

Doublet combination of Lenalidomide and dexamethasone (Rd) remains an accepted first-line induction regimen and is reimbursed by the PBS for transplant ineligible patients based on the phase III FIRST (Frontline Investigation of Revlimid and dexamethasone versus Standard Thalidomide) clinical study[96]. Here, continuous Rd (i.e. Rd until disease progression) was superior to MPT (melphalan, prednisone and thalidomide) with respect to PFS (4 year PFS 32.6 vs. 16.6 months (MPT), p<0.00001) and OS (predicted 4 year OS: 59% vs. 51% (MPT), p=0.0023)[97]. Continuous Rd significantly improved PFS over fixed duration (18 months) Rd. Four year PFS was 32.6 months with continuous Rd vs. 14.3 months with fixed duration Rd. However, OS was similar (predicted 4-year OS: 59m (cont. Rd) vs. 58m (18m Rd), respectively). This may be partly explained by the fact that a significant proportion of patients in the fixed duration Rd arm were retreated with Rd again upon first relapse.

Of note, Rd doublet is not necessarily inferior to lenalidomide containing triplet combinations with chemotherapy, which is more toxic for elderly patients. In the MM015 study, lenalidomide plus melphalan and prednisolone (MPR) was less well tolerated in elderly patients age >75 years, mainly due to myelosuppression, resulting in no PFS improvement over MP in this subgroup of patients[98]. In other studies, the addition of an alkylating agent (cyclophosphamide or melphalan) to Rd has not been found to improve ORR, PFS or OS in first line treatment of transplant ineligible patients[99]; when combined with Rd, melphalan is more myelotoxic compared to cyclophosphamide.

In contrast to Rd, doublet Vd is generally inferior to bortezomib-containing triplet combinations with chemotherapy. Doublet Vd is efficacious for patients who are unfit for triplet therapy with an expected ORR and CR of up to 70% and 25%, respectively[100].

Unlike lenalidomide or bortezomib, thalidomide-dexamethasone (Td) doublet therapy is not superior to MP, resulting in similar PFS (16.7 vs. 20.7m, p=0.1)[101]. In fact, OS is shorter with Td compared to MP due to greater toxicities particularly in patients aged ≥75 years with poor performance status. Thus, when thalidomide is used, it is often used in triplet combination (eg. CTD or MPT) rather than doublet combination (Td). In the First (MM020) study, MPT was demonstrated to be inferior to Rd and so should be only used if lenalidomide or bortezomib combinations are contraindicated.

Table 7B outlines the more common induction treatment regimens for transplant ineligible patients. Recommendations for initial induction therapy for transplant ineligible patients are summarised in box 8.

Table 7B: Induction therapy for patients not proceeding to stem cell transplant.

REGIMEN	SCHEDULE	COMMENTS
VRd		Please see section 3.2.2.2 for detailed discussion. - subcutaneous bortezomib preferential to intravenous administration to minimise peripheral neuropathy - Vigilance is required for the development of peripheral neuropathy. Prompt withholding of bortezomib and/or dose reduction is required in the event of grade 3 (CTCAE) peripheral neuropathy particularly if there is burning/pain to avoid irreversibility. Alternatively, a weekly schedule of subcutaneous bortezomib may be adopted at the outset as it is better tolerated than intravenous (IV) and will unlikely compromise efficacy [57, 93]. - If a patient is deemed suitable for the schedule as outlined in the SWOG-SO777 study, consider proceeding with upfront ASCT. - Note that VRd-lite has only been studied in a phase II single arm trial of 50 patients. - Rd is a well-tolerated and widely accepted standard of care for initial treatment of TIE patients based on the phase III FIRST study. - In the phase III MAIA study[96], the addition of Daratumumab to Rd (DaraRd) resulted a superior PFS (HR 0.53, p<0.0001) and OS (HR 0.68, p=0.013) . - As of January 2022, DRd is TGA-registered but not PBS reimbursed for the initial treatment of TIE patients with MM.
SWOG SO777[88] (phase III RCT)	**Induction:** Eight 21-day VRd cycle: V: 1.3mg/m2 IV D1,4,8,11 R: 25mg po D1-14 d: 20mg D1,2,4,5,8,9,11,12 followed by**Rd maintenance** until disease progression.: 28-day cycle. R: 25mg po D1-21 d: 40mg po D1,8,15,22	
VRD-Lite		
VRd-lite[52]	**Induction:** Nine 35-day cycles of: V: 1.3mg/m^{2}sc D 1,8,15,22 R: 15mg po D1-21 d: 20mg D1,2,8,9,16,16,22,23 Followed by **consolidation:** Six 28-day cycles of: V: 1.3mg/m^{2}D1,15 R: 15mg po D1-21	
Rd		
Rd[96, 163]	R: 25mg po daily, days 1-21. d 40mg po daily, days 1,8,15,22 28-day cycles repeated every 4 weeks. Treatment until disease progression.	

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REGIMEN	SCHEDULE	COMMENTS
VMP		MSAG comments: - For bortezomib- containing regimens, weekly bortezomib improves tolerability in transplant ineligible patients without compromising efficacy. Thus, weekly bortezomib 1.3mg/m^2 schedule is acceptable. - Subcutaneous bortezomib is recommended as its efficacy is non-inferior to IV bortezomib but has an improved toxicity profile[93]. - In the ALCYONE study, the addition of daratumumab to VMP (DaraVMP) resulted in superior depth of responses and PFS (HR 0,5, p<0.001) compared to VMP. As of January 2022, Dara-VMP is TGA-registered but is not PBS reimbursed for the initial treatment of TIE patients with MM. The use of cyclophosphamide in place of melphalan is of comparable efficacy[56].
VMP[164]	Nine 6-week cycles of VMP: V: 1.3 mg/m^2 IV days 1, 4, 8, 11, 22, 25, 29, and 32 (cycles one to four) and days 1, 8, 22, and 29 (cycles five to nine) M: 9mg/m^2 orally D1-4 P: 60mg/m^2 orally D 1-4	
VCd		
VCd[56]	Up to twelve 28-day cycles. V: 1.3mg/m^2 IV D1,8,15,22 C: 300mg/m^2 orally D1,8,15,22 d: 40mg orally D1,8,15,22	
Vd		
Vd[101]	V: 1.3 mg/m^2 IV D1, 4, 8, and 11 IV every 3 weeks d: 40mg orally on day of and day post bortezomib.	

RCT: randomised controlled trial; V: bortezomib; R: lenalidomide; d: dexamethasone; T: thalidomide; Mel: melphalan; dara: daratumumab; IV: intravenous; po: oral; sc: subcutaneous

Box 8. Recommendations for initial induction therapy for transplant ineligible patients.

- *The current accepted standard of care for the initial treatment of transplant ineligible patients with multiple myeloma include:*
  - *Bortezomib, lenalidomide and dexamethasone (BLd), once it is reimbursed by the Australian PBS* (Level 1B evidence, grade A recommendation)*
    - *BLd-lite appears to have comparable efficacy with reduced toxicity, in particular, reduced peripheral neuropathy (Level 2A evidence, grade B recommendation).*
  - *Continuous lenalidomide and dexamethasone (Ld) (Level 1B evidence, grade A recommendation).*
  - *Bortezomib, melphalan and prednisolone (BMP) (level 1B evidence, grade A recommendation.*
    - *Cyclophosphamide could be substituted for melphalan (CyBorD regimen)*
    - *For unfit elderly patients (section 3.3.1), bortezomib and dexamethasone (Bd) as doublet should be considered (level 1B, grade B recommendation)*
    - *For bortezomib, a weekly schedule is recommended for transplant ineligible patients.*
- *Thalidomide, melphalan and prednisolone (MPT) has now been shown to be inferior to Ld (Level 1B evidence) and should only be used if only used if lenalidomide or bortezomib combinations are contraindicated (Grade A recommendation).*

** At the time of publication of this guideline, combination BLd received positive recommendation by the Australian PBAC for the upfront treatment of transplant ineligible patients with multiple myeloma, and is anticipated to be reimbursed on the PBS in the near future.*

3.2.2.3 Dose attenuation in unfit elderly patients

Treatment-related toxicities and early treatment discontinuation have each been shown to be associated with shorter survival in elderly patients with MM[80], highlighting the need for treatment dose-attenuation particularly in the unfit elderly patient (table 9).

For bortezomib, the weekly schedule (as opposed to days 1,4,8,11 every 21 days) significantly reduces the rate of grade ≥3 peripheral neuropathy from 28% to 8% without impact on efficacy[91]. In addition, one randomised trial in patients with RRMM has shown that the subcutaneous route of administration was associated with reduced peripheral neuropathy without compromising efficacy[92]. In patients aged above 75 years, low-dose thalidomide (50-100mg) is more tolerable than doses of 200mg or more. Similarly, lower-dose oral melphalan (0.18-0.2mg as opposed to 0.25mg per kg) is safer in this age group such that the best MPT result in patients aged above 75 years was achieved with reduced-dose thalidomide and melphalan[102].

High-dose dexamethasone (40mg days 1-4, 9-12, 17-22) is associated with significant toxicities in elderly patients, and this has been shown to decrease OS compared to lower dose dexamethasone (40mg weekly)[50]. For patients older than 75 years or who are frail, a lower starting dose of dexamethasone, 20mg weekly, should be considered[82].

Standard-dose lenalidomide (25mg) is generally well tolerated in elderly patients. However, dose reduction is recommended in patients with impaired renal function. Finally, lenalidomide at 10mg, when combined with melphalan and prednisone (MPR) did not improve PFS, as compared with MP, in patients age ≥75 years, but dose reductions were required more frequently than for younger patients [98].

Table 8: Selected regimens for the treatment of relapsed/refractory multiple myeloma in Australia.

REGIMEN	SCHEDULE	COMMENTS
Bortezomib-based		
DaraVd[1] Daratumumab + Bortezomib + Dexamethasone (CASTOR study)	Eight 21-day cycles of DaraVd followed by dara until PD: Dara: 16mg/kg IV QW cycles 1-3, Q3W cycles 4-8, then Q4W until PD V: 1.3mg/m^2 IV D1,4,8,11, cycles 1-8 D: 20mg po1,2,4,5,8,9,11,12. Cycles 1-8	Refer to section 4.3 for detailed discussion. **Dara-Vd** is PBS-reimbursed only for patients who have had 1 prior line of therapy Subcutaneous Dara (fixed dose 1800mg) can be substituted for IV Dara.
PVd[4] Pomalidomide + Bortezomib + Dexamethasone (OPTIMISMM study)	21-day cycles until disease progression. P: 4mg po days 1-14 V: 1.3mg/m^2 IV D1,4,8,11, cycles 1-8 D1, 8, cycles 9+ D: 20mg (10mg for age over 75 years) on day of and day post bortezomib)	**PVd** is PBS-reimbursed for patients who have had at least 1 prior line of therapy
VCd[5] Bortezomib + Cyclophosphamide+ Dexamethasone	21 to 35-day cycles until disease progression V: 1.3mg/m^2 IV D1,4,8,11 every 21 days, for cycles 1-8; D1,8,15,22 every 35 days, for cycles 9-14. C: 300mg/m^{2}po. weekly. D: 20mg on the day of and day after bortezomib	Vigilance for peripheral neuropathy is required with bortezomib. Weekly schedule of subcutaneous of bortezomib is better tolerated than twice-weekly or intravenous (IV) bortezomib, and can be used at the clinician's discretion [2, 3].
Vd: Bortezomib + Dexamethasone (APEX study) **[6]**	21-day cycles until disease progression V: 1.3mg/m^2 IV D1,4,8,11 every 21 day for cycles 1-8; D 1,8,15,22 every 35 day for cycles 9-12 D: 20mg po. on day of and day after bortezomib.	

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REGIMEN	SCHEDULE	COMMENTS
Carfilzomib-based		
Kd: Carfilzomib + Dexamethasone [7] (ENDEAVOR study)	28-day cycles until disease progression K: 20mg/m^2 IV C1D1,2 56mg/m2 IV C1D8,9,15,16 C2+: K 56mg/m2 IV D1,2,8,9,15,16 d: 20mg po day of and day after K.	**Kd** is PBS reimbursable for patients who have had at least 1 prior line of treatment As of March 2022, **KRd** received positive PBAC recommendation for the treatment of patients who have had at least 1 prior line of therapy but is yet to be reimbursed by the PBS as of June 2022 **KTd** may be an alternative to KRd in patients who cannot receive lenalidomide due to severe renal impairment. The use of thalidomide in combination with carfilzomib is not reimbursed by the PBS as of June 2022. Consider non-PBS funding for thalidomide as it is a relatively low-cost IMiD. When combined with dexamethasone, once weekly schedule of K 20/70mg per m^2 has been shown to have equivalent efficacy and reduced adverse events compared to twice-weekly K 20/27mg per m^2. However, the weekly schedule has not been directly compared to the twice-weekly 20/56mg per m^2 schedule. Weekly carfilzomib (56mg/m^2 on days 1,8,15 in a 28-day cycle) has been shown to be safe when used in a triplet regimen[8], and can be used instead of a twice weekly schedule at the clinician's discretion
KRd: Carfilzomib + Lenalidomide + Dexamethasone[9] (ASPIRE study)	28 day cycles until disease progression. K: 20mg/m^2 IV C1D1,2 27mg/m2 IV C1D8,9,15,16 C2+: K 27mg/m2 IV D1,2,8,9,15,16 R: 25mg po daily d: 40mg po D1, 8,15,22 After 12 cycles, carfilzomib is given on days 1,2,15,16 until cycle 18, then stop, and lenalidomide is continued until disease progression.	
KTd[10] Carfilzomib + Thalidomide + Dexamethasone (ALLG MM018 study)	28-day cycles until disease progression K: 20mg/m^2 IV C1D1,2 56mg/m2 IV C1D8,9,15,16 C2+: K 56mg/m2 IV D1,2,8,9,15,16 T: 100mg po daily d: 40mg po D1, 8,15,22	
KCd [11] Carfilzomib + Cyclophosphamide + Dexamethasone	Six 28-day cycles of KCd followed by carfilzomib-dexamethasone (Kd) maintenance until disease progression. K: 20mg/m^2 IV D1,2 36mg/m^2 IV D8,9,15,16 C: 500mg/m^2 po D1,8,15 D: 40mg po D1,8,15	

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REGIMEN	SCHEDULE	COMMENTS
Lenalidomide-based		
Rd[12] Lenalidomide + Dexamethasone	28-day cycles until disease progression R: 25mgpo. D1-21q28 d: po. D1-4,9-12,17-20 (C1-4), 40mg po. D1-4 (C5 onwards)	Consider using low dose dexamethasone (40mg per week) in view of the ECOG trial showing higher toxicity compared with pulse-dose dex[13]
RCd[14] Lenalidomide + Cyclophosphamide + Dexamethasone	Eight 28-day cycles of RCd followed by Rd until disease progression. R: 25mg po. D1-21. C: 500mg po weekly d: 40mg po weekly.	
Elo-Rd[15] Elotuzumab+ Lenalidomide + Dexamethasone (ELOQUENT-2 study)	28-day cycles until disease progression. Elo: 10mg/kg IV weekly cycles 1,2 Every 2 weeks cycles 3+ R: 25mg po D1-21 D: 40mg po weekly	
Pomalidomide-based		
Pd[16]: Pomalidomide + Dexamethasone (MM-003 study)	28-day cycles until disease progression P: 4mg po. D1-21 d: 40mg po D1,8,15,22	
Selinexor-based		
Xd[17]: Selinexor Dexamethasone (STORM study)	28-day cycles until disease progression X: 80mg po days 1+3 every week D: 20mg po days 1+3 every week	As of March 2022, Xd received positive PBAC recommendation for the treatment of patients with triple class refractory and Penta-refractory MM Supportive care including regular anti-emetics is important especially in the first 2 cycles, which can be used as required thereafter.

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REGIMEN	SCHEDULE	COMMENTS
Chemotherapy-based		
DTPACE [**5**]	Three to six 28-day cycles. Dexamethasone: 40mg po. D1-4 Thalidomide: 400mg po.daily Cisplatin: 10mg/m^2 daily IV continuous infusion D1-4. Cyclophosphamide: 400mg/m^2 daily IV continuous infusion D1-4. Etoposide: 40mg/m^2 daily IV continuous infusion D1-4. Doxorubicin: 10mg/m^2 daily IV continuous infusion D1-4.	The use of thalidomide at doses above 200mg is not well-tolerated, mainly due to peripheral neuropathy. An alternative dose of 100-200mg per day is acceptable.
DCEP-T**[18]**	Three to six 28-day cycles. Dexamethasone: 40mg po. D1-4 Thalidomide: 400mg po.daily Cisplatin: 15mg/m^2 daily IV continuous infusion D1-4. Cyclophosphamide: 400mg/m^2 daily IV continuous infusion D1-4. Etoposide: 40mg/m^2 daily IV continuous infusion D1-4.	
Non-myeloablative melphalan[19]	Melphalan 25mg/m^2 IV	
High dose cyclophosphamide [20]	Cyclophosphamide 600mg/m^2 IV daily x 4 (total dose 2400mg/m^2) Or Single dose of 2 to 4g/m^2 IV	
Bendamustine[21]	Bendamustine 60-100mg/m^2 IV D1, 2 of each 28-day cycle.	

V: bortezomib; R: lenalidomide; K: carfilzomib; P: pom; C: cyclophosphamide; d: dexamethasone; T: thalidomide; Mel: melphalan; dara: daratumumab; Elo: Elotuzumab; IV: intravenous; po: oral; sc: subcutaneous

Table 9: Recommended dose attenuation in unfit elderly patients.

	65-75 years (standard dose)	>75 years or unfit 65-75years (reduced dose)
Dexamethasone weekly	40mg	20mg
Bortezomib	1.3mg/m^2 weekly Subcutaneous route.	1.3mg/m^2 weekly Prompt dose-reduction to 1.0mg/m^2 weekly upon side effects. Subcutaneous route.
Lenalidomide	25mg	15-25mg*
Melphalan days 1-4	0.25mg/kg	0.12-0.18mg/kg
Cyclophosphamide weekly	300mg/m^2	150mg/ m^2
Thalidomide (per day)	100mg	50-100mg

* Elderly patients are more susceptible to lenalidomide-induced myelosuppression. suggest close monitoring at the commencement of treatment and prompt dose reduction in the event of toxicity. A lower starting dose is required for patients with CrCL≤ 60ml/min.

3.2.3 Patients with high-risk MM

Several factors are known to confer a poorer prognosis in patients with MM (table 6). These include older age [103], high B_2-microglobulin level, low albumin level, high LDH, high plasma cell labelling index and the cytogenetic abnormalities: t(4;14), t(4;16) and 17p deletion (as identified by FISH) [104-106], 13q deletion (identified by standard cytogenetics), as well as hypodiploidy and complex (combination of ≥3) cytogenetic abnormalities. Amplification of chromosome 1q21 (by FISH) has also been shown to be associated with both shorter time to disease progression and poorer prognosis[107, 108].

In the assessment of primary genetic abnormalities, FISH remains the standard technique, whereas molecular approaches including various gene expression profile including the validated EMA/FDA approved SKY92 MM profiler{van Beers, 2021 #2668} are only used in the context of clinical studies [109].

In the era of IMIDs and PIs, patients with high-risk MM are defined as those with an expected OS of <3 years for transplant eligible or <2 years for transplant ineligible. For transplant eligible patients, those with an expected OS <2 years are classified as “ultra-high-risk”[6, 109]. The most robust factors that are consistently associated with such poor survival are higher ISS stage and the cytogenetic abnormalities 17p deletion and t(4;14). The revised(R)-ISS risk stratification system now incorporates ISS stage, LDH and high-risk FISH (del17p and t(4;14)),(table 5). In the era of IMiDs and PIs, the R-ISS can clearly identify 3 different MM prognostic groups in patients and now supersedes the previous ISS staging system[6, 110].

With respect to treatment, thalidomide does not overcome HR cytogenetic abnormalities. Several reports have confirmed that bortezomib improves PFS and OS in the presence of poor risk cytogenetics (13q deletion, t(4;14), amp1q21, and perhaps even 17p deletion) [108, 111-114] although it does not overcome the entire adverse impact of these mutations, especially when t(4;14) and del17p are combined[46].

There are limited data for lenalidomide in patients with high-risk cytogenetics. For transplant eligible patients, lenalidomide maintenance post ASCT appears to improve PFS but not OS for t(4;14) and del17p lesions [32, 115-117]. For transplant ineligible patients, results from the major phase III studies of lenalidomide (MM015[98] and FIRST[96]) showed no strong evidence that continuous lenalidomide can curb the impact of high-risk cytogenetics. Limited data exist for pomalidomide[118]. There are some data supporting the combined used of bortezomib and lenalidomide in patients with high-risk cytogenetics[60, 119], however, most of these data are from small non-randomised studies and further confirmation is required.

Tandem ASCT may have a role in patients with poor prognostic features, as was suggested in an integrated analysis of phase III European studies, in which patients were prospectively assigned to receive either single or tandem ASCT. Tandem ASCT resulted in OS benefit compared to single ASCT, that was particularly evident in patients with high-risk cytogenetics and who failed to achieve CR post bortezomib-based induction (5-year OS estimate 70% vs. 17% with single ASCT, p<0.001[43].

The role of AlloSCT in patients with high-risk MM remains uncertain as the data are scarce. In one retrospective study of 143 patients, the PFS and OS of patients with high-risk cytogenetics (del13q, t(4;14) and del17p) was similar to those without these high-risk lesions. In another prospective study of 101 patients in the RRMM setting, alloSCT appeared to overcome the negative prognostic impact of t(4;14) but not del17p, with respect to PFS and OS. Nonetheless, numbers were small in this study. Due to the heterogeneity of these trials, no firm conclusion can yet be made and AlloSCT remains an area of active investigation. Importantly, optimal results from either tandem ASCT or alloSCT are seen in early phase of the disease, hence early referral to a transplant physician is important.

Recommendations for patients with high-risk MM are summarised in box 9.

Box 9: Recommendations for patients with high risk MM:

Although there are a number of prognostication models, in the clinic, the R-ISS (table 4) is an accepted risk stratification approach to identify patient with high-risk MM. Patients with R-ISS 3 are considered high-risk with a median OS <2 years in the era of IMiDs and PIs.

The optimal management for patients with high-risk multiple myeloma remains unclear in the absence of definitive trial data.

- *Combination bortezomib and lenalidomide (VRd), or if not, at least bortezomib-based regimen as part of induction treatment is recommended (grade A recommendation, level 1B evidence)*
- *Consider tandem autologous stem cell transplant, especially in patients who have not achieved a CR to bortezomib-based induction or first ASCT (grade B recommendation, level 2A evidence)*
- *Consider early referral for allogeneic stem cell transplant consideration for selected patients with HLA-matched sibling. However, the role of allogeneic stem cell transplant, even in the high-risk setting is still unclear and requires discussions with both the transplant and treating haematologist early in the disease course (grade C recommendation, level 4 evidence)*

3.3 CONSOLIDATION/MAINTENANCE THERAPY

3.3.1 Consolidation and maintenance therapy post ASCT

Consolidation following ASCT refers to a short treatment-course (2 to 4 cycles) to improve depth of response[59]. To date, there has been insufficient data to determine whether a consolidation improves overall survival; studies of consolidation post ASCT demonstrate improvement in depths of responses and PFS but none of which have shown OS benefit [59, 119]. The phase III BMT CTN StaMINA study looked specifically at the role of consolidation. Patients aged <71 years (n=758) were randomised after induction, 1:1:1 to either single ASCT, or consolidation with either a second (tandem) ASCT or 4 cycles of RVd (lenalidomide, bortezomib, dexamethasone), prior to maintenance lenalidomide therapy. The addition of consolidation, whether it be a second ASCT or 4 cycles of RVd was not found to be superior to no consolidation with respect to PFS or OS. Thus, if one gives effective induction and lenalidomide maintenance post ASCT, then there is little incremental benefit with consolidation.

In contrast to consolidation, maintenance therapy with lenalidomide post ASCT has been shown to improve PFS and OS based on meta-analysis of 3 large phase III randomised studies: CALBG (n=460), IFM (n=614) and GIMEMA (n=134) [120]. Grade ≥3 neutropenia is the most frequent adverse event. Lenalidomide related secondary malignancies ([7.8-8.5% lenalidomide vs. approximately 3% placebo] was an initial concern, however, meta-analysis has shown that the risk pertains mainly to secondary haematological malignancies and is closely related to the use of oral melphalan[121]. The current general consensus is that the benefits of lenalidomide treatment until disease progression outweighs the risks. Lenalidomide monotherapy is reimbursed on the PBS for maintenance therapy post ASCT

Bortezomib likely improves depth of response when used as consolidation or maintenance. However, the design of available studies, which incorporated different induction and consolidation arms make it difficult to elucidate the impact of bortezomib maintenance on survival[111]. As such, no firm conclusions regarding bortezomib consolidation or maintenance can be made. Importantly, the final results from the Australian phase III VCAT study (Bortezomib Consolidation with Thalidomide and Prednisolone Vs Thalidomide and Prednisolone Alone in Previously Untreated Subjects With Multiple Myeloma After VCD Induction and ASCT), showed the addition of bortezomib (1.3mg/m2) every two weeks for 32 weeks to thalidomide+prednisolone resulted in a non-statistically significant higher depth of response (≥VGPR 85.7% vs. 77.1%), that did not translate to an improved PFS or disease free survival[122]. The concurrent use of thalidomide and bortezomib is not reimbursed on PBS in Australia.

Ixazomib, a second generation orally bioavailable PI, is also proven effective as maintenance post ASCT. In the TOURMALINE-MM3 study, ixazomib (4mg [3mg in the first 4 cycles] po weekly for 3 weeks in a 4 week cycle) in a fixed 2-year maintenance pot ASCT, resulted in superior PFS (HR 0.72, p-0.002) compared to placebo[123]. In the absence of evidence for OS advantage, perhaps due to short follow up (median 30.9 months), ixazomib cannot be recommended over lenalidomide, but may be a viable alternative for patients who cannot tolerate the latter. In Australia Ixazomib is neither registered by the TGA nor reimbursed for maintenance therapy in MM.

Box 9 outlines the recommendation for consolidation and maintenance therapy post ASCT.

Box 10: Recommendations regarding consolidation and maintenance therapy post ASCT:

- *Consolidation therapy (typically 2-4 cycles) post ASCT is not routinely recommended in Australia as there is not yet firm evidence to show that it improves survival, especially when effective induction (incorporating either IMiDs and/or PIs) before and maintenance post ASCT is given (grade B recommendation, level 2A evidence).*
  - *For TE patients, the Australian PBS reimburse sufficient VRd to allow for 2 cycles of VRd consolidation post ASCT. Clinicians may choose to use consolidation to deepen response in patients who has achieved <CR post ASCT, however, there is no firm evidence to show that this will improve survival.*
- *Lenalidomide maintenance post ASCT improves PFS and OS, and is recommended for maintenance post ASCT in Australia once it is reimbursed on PBS for this indication (Grade A recommendation, level 1A evidence)*
- *The dose schedule and role of maintenance bortezomib is still unclear, and bortezomib is not TGA registered nor PBS reimbursed for this indication. Bortezomib maintenance post ASCT is not routinely recommended. (Grade C recommendation, level 4 evidence)*
- *Ixazomib maintenance post ASCT improves PFS (level 1B evidence), but lacking data for OS. Ixazomib cannot be recommended over lenalidomide for maintenance post ASCT, but may be a viable alternative maintenance. Currently ixazomib is neither registered by TGA nor reimbursed by PBS for this indication in Australia.*

3.3.2 Maintenance therapy for patients not eligible for stem cell transplants

Continuous therapy beyond the induction phase of treatment for transplant ineligible patients has been shown to improve PFS. The strongest evidence exists for lenalidomide. Three pivotal randomised phase III trials have demonstrated the benefit of continuous lenalidomide beyond induction. In a pre-specified landmark analysis of the MM015 trial that compared MP vs. MPR vs. MPR with ongoing lenalidomide maintenance (MPR-R), lenalidomide maintenance improved PFS by 17 months, but not overall survival [98]. In the final analysis of the FIRST trial, continuous Rd until disease progression improved both PFS and OS compared to a fixed duration MPT (HR 0.69, p<0.00001 and HR 0.78, p=0.0023, respectively). Rd until disease progression was superior to fixed duration Rd (18 months) with respect to PFS (HR 0.7) but not OS[97].

For elderly, intermediate fit patients with NDMM, preliminary data from the phase III RV-MM-PI-0752 study{Larocca, 2018 #2669} demonstrated that after 9 cycles of induction with standard Rd (lenalidomide 25mg po D1-21q28 days and weekly dexamethasone 20mg po), continuation of a lower dose of lenalidomide (10mg) without dexamethasone resulted in similar efficacy but with potentially improved tolerability compared to continuation with standard dose Rd until disease progression.

For transplant ineligible patients who received thalidomide or bortezomib during induction, the phase III Myeloma XI study (CTd or CRd induction followed by bortezomib-based salvage versus placebo upon inadequate response, then lenalidomide versus placebo maintenance post induction) indicated benefit of lenalidomide maintenance over placebo with respect to PFS (HR 0.44 in the NTE cohort, p 0.014) but not yet OS after a median follow up of 31 months[124].

In Australia, lenalidomide is reimbursed by the PBS for continuous treatment until disease progression when Rd is used as initial treatment in NTE patients, but not for maintenance post induction therapy with a non-lenalidomide containing regimen.

With respect to bortezomib maintenance for transplant ineligible patients, two randomised studies have been reported. However, these trials were not designed to assess the isolated impact of bortezomib maintenance. The GIMEMA study compared VMPT followed by VT maintenance to VMP alone. BT maintenance improved CR rate slightly from 58% (post BMPT induction) to 62%; 3-year PFS was higher in the BMPT-BT arm (56 vs. 41%, p=0.008). Five year OS was superior in the VMPT-BT arm compared to BMP (59 vs. 46%, p=0.04)[125]. The PETHEMA study compared BMP to BTP induction followed by BT or BP maintenance. Maintenance therapy overall improved CR rate from 24 to an astounding 42%[90] but no difference with respect to PFS or OS was seen between BP or BT maintenance. Recommendations on maintenance therapy in patients who are not transplant eligible are summarised in box 11.

Box 11: Recommendations on maintenance therapy in patients with MM who are not transplant eligible:

- *Continuous therapy beyond initial induction, until disease progression has been shown to improve PFS for transplant ineligible patients.*
  - *For patients who are treated with Rd, VRd or VRd-lite, we recommend that lenalidomide be continued beyond initial induction, until disease progression (level 1B evidence, grade A recommendation)*
    - *For elderly, intermediate fit patients, omission of dexamethasone and dose attenuation of lenalidomide during the maintenance phase (after 9 cycles of Rd or 8 cycles of VRd/VRd-lite) to 10mg is not unreasonable especially in the context of poor tolerance.*
  - *For transplant ineligible patients initially treated with a non-lenalidomide containing regimen, maintenance lenalidomide has been shown improve PFS (Level 1B evidence, grade A recommendation). However in In Australia, lenalidomide is not registered nor reimbursed by the PBS for maintenance therapy post thalidomide or bortezomib-based induction for TIE patients.*
- *The benefit of bortezomib maintenance therapy is unclear, while ixazomib maintenance post induction therapy improves PFS but not OS for transplant ineligible patients. Neither bortezomib or ixazomib is TGA-registered nor reimbursed for this indication and is therefore not routinely recommended (Grade A recommendation, level 1B evidence)*

3.4 RELAPSED REFRACTORY MULTIPLE MYELOMA:

Relapsed MM refers to myeloma that has progressed after an initial response, relapsed refractory MM (RRMM) refers to progression on treatment or within 60 days of cessation of the most recent treatment after having achieved at least a minor response, while primary refractory MM refers to the failure to achieve at least a minor response to a given treatment. These terminologies are defined as per IMWG criteria[126].

Many but not all patients will require immediate treatment at first detection of relapse. For patients with relapse with worsening or new CRAB symptoms, immediate treatment is mandatory. In the absence of worsening or new CRAB symptoms, immediate treatment may also be warranted in patients with rapidly progressive paraprotein level or SFLC (table 10), to prevent the onset of irreversible end organ damage. Otherwise, for patients with slow indolent biochemical relapse without any overt worsening or new CRAB symptoms, careful monitoring until significant progression occurs is acceptable.

Table 10: Indications to commence treatment for myeloma at relapse[127].

CLINICAL RELAPSE: • Development of new soft tissue plasmacytomas or bone lesions • Definite increased (≥50%) size of existing plasmacytomas or bone lesions. • Hypercalcaemia (≥11.5mg/dl; 2.875mmol/l) • Decrease in haemoglobin by ≥20g/L or to <100g/L due to myeloma. • Rise in serum creatinine by >177 µmol/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 ≥10g/L or ◦ **The increase of urinary M protein (BJP) by** ≥0.5g per 24 hours or ◦ **Increase of involved FLC level by** ≥200mg/L (with abnormal K:L ratio) or 25% increase (whichever is greater).

Treatment of patients with relapsed refractory multiple myeloma

There is no standard sequence or algorithm of treatment for patients with relapsed and/or refractory MM. The choice of salvage regimen depends on patient factors (age and frailty), disease factors (tempo of relapse, risk-group stratification), and prior treatment-related factors (response or refractoriness to prior type of treatment). The first 3 lines of treatment are perhaps the most important in dictating a person's overall survival, as not many patients reach 4th line treatment and beyond. According to the Australian and New Zealand MRDR (www.mrdr.net.au), less than 40% of people with MM reach 4th line therapy. Thus, the most effective treatment option should be used as early as possible and not saved for the purpose of expanding subsequent treatment options..

In Australia, the main treatment options for relapsed/refractory MM are combinations incorporating IMiDs (thalidomide, lenalidomide and pomalidomide), PI (bortezomib and carfilzomib), anti-CD38 mAb (daratumumab), alkylating agents, anthracyclines, and corticosteroids, with selected patients undergoing HDT with ASCT. These various agents can be used in various combinations within PBS restrictions (please refer to www.pbs.gov.au), and in different sequences. No best sequence has been defined (Figure 4; box 12; table 8).

We recommend enrolment into a clinical trial if one is available as first option. Otherwise, the generally accepted principles are as follows:

- Switch drug class, especially if remission to prior drugs was short or patient had concerning associated toxicity.
  - Retreatment with a prior line of treatment is feasible if a long prior remission (eg. treatment free interval >1 year), was achieved with no concerning toxicity. However, an inferior duration and quality of response is to be expected.
- HDT and ASCT can be considered in patients who have had a deep (at least PR) and durable response to this treatment modality in the past[128]. Data from the British Blood and Bone Marrow Transplant Registry suggested that a PFS of at least 9 months to the first ASCT is associated with improved survival outcome to a second ASCT in relapsed MM [128].
- In patients with rapidly progressive disease, regimens combining an IMiD and/or PI with either a mAb or one or more chemotherapy (table 8) can be considered. In contrast, in patients with a slow tempo of disease relapse, doublet PI or IMID with dexamethasone, or indeed ongoing observation in the absence of end-organ damage may be appropriate, especially if they cannot tolerate more intensive treatment.

- Finally, when all newer agents and different treatment combinations have been exhausted, conventional doses of cyclophosphamide[129], non-myeloablative doses of melphalan[130], or low-modest doses of corticosteroids remain viable options, as is palliation in patients who cannot tolerate any further therapy. Please see box 12.

In addition to these general principles, the choice of salvage also depends on pre-existing co-morbidities.

- In patients with pre-existing neuropathy, bortezomib or thalidomide should be used with caution or avoided if other options exist.
- For patients with a previous history of VTE, or who are at high-risk of VTE events, prophylactic or therapeutic anticoagulation is important with IMIDs and should be as per clinical indication. VTE risks are highest when these immunomodulatory drugs are used with high-dose dexamethasone or anthracycline chemotherapy.
- Lenalidomide (but not pomalidomide or thalidomide) is renally excreted, and generally, is not the treatment of first choice in patients with moderate to severe renal impairment although judicious dose adjustment can overcome this issue[131].
- Uncontrolled hypertension (especially CTCAE grade 3 [≥ 160mmHg systolic or ≥100 mmHg diastolic] should be controlled adequately before commencing carfilzomib. During carfilzomib therapy, blood pressure should be monitored and controlled ideally to less than CTCAE grade 2 (≤ 140 mmHg systolic and ≤90mmHg diastolic).
- Carfilzomib should be used with caution in patients with known pulmonary hypertension or uncontrolled cardiac disease.

Treatment of patients with relapsed and/or refractory MM after 1 to 3 prior lines of treatment:

In Australia, the PBS-reimbursed treatment regimens that are most often considered for patients who have relapsed after 1 to 3 prior lines of therapy ***include Kd (carfilzomib and dexamethasone)***, ***PVd (pomalidomide, bortezomib, and dexamethasone)***, and ***Dara-Vd (daratumumab, bortezomib, dexamethasone)***. The latter is only reimbursed for patients with 1 prior line of therapy.

Kd *is reimbursed on the PBS for patients who have had at least 1 prior line of treatment*, based on the phase III Endeavor study that showed superiority of Kd compared to bortezomib and dexamethasone (Vd) with respect to PFS (HR 0.53, p<0.0001) and OS (HR 0.79, p=0.01)[132]. Carfilzomib was given at a dose of 20/56mg per m2 (ie. 20mg/m2 cycle 1 day 1 then 56mg/m2 cycle 1 day 8 onwards) at the standard twice-weekly schedule on days 1,2,8,9,15,16 in a 28-day cycle. Of note, the phase III randomised ARROW study showed that weekly schedule of carfilzomib 20/70mg per m2 (ie. 20mg/m2 cycle 1 day 1 then 70mg/m2 cycle 1 day 8 onwards) was just as effective as twice weekly 20/27mg per m2 (ie. 20mg/m2 cycle 1 day 1 then 27mg/m2 cycle 1 day 8 onwards) with respect to response rates and PFS, and with improved safety profile. However, the once weekly 20/70mg per per m2 schedule should not be assumed to be equivalent to a twice weekly 20/56mg per m2 when carfilzomib is used as doublet therapy with dexamethasone, as is in the Endeavor study. On subgroup analysis, the relative superiority of Kd compared to Vd was greatest in patients with 1 prior line of treatment (med PFS 22m vs. 10m, HR 0.447, p<0.001) and was evident in patients who were bortezomib exposed (med PFS 10.6m vs. 8.1m, HR 0.688, p=0.0052) or lenalidomide exposed/refractory (med PFS 12.9m vs. 7.3m, HR 0.688, p=0.0052)[133]. Thus, Kd is an effective salvage regimen for patients who have relapsed post initial bortezomib and/or lenalidomide containing therapy.

The addition of cyclophosphamide to Kd (**KCd**) is safe and effective; preliminary data from the UK Muk Five study demonstrated superiority of KCd over VCd with respect to rate and depth of response in patients with 1st relapse (ORR 84% (KCd) vs. 68.1% (VCd), p=0.001), particularly those with high-risk cytogenetics del17p. 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)[134]. In combination with thalidomide and dexamethasone (**KTd**), the Australian ALLG MM018 study demonstrated high ORR (82%; ≥VGPR 65%; CR 16%) with a median PFS not reached after median follow up of 7.2m (1 year PFS 67.7%)[135]. Of note, thalidomide is not reimbursed by PBS when used in combination with carfilzomib.

The most common side effects of carfilzomib are hypertension (14% grade≥3), fatigue (7% grade≥3), dypsnoea (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)[136]. 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, the OPTIMISMM study was carried out only in patients with 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.

Dara-Vd *is reimbursed by the PBS only for patients who have had 1 prior line of therapy*, based on the phase III CASTOR study[137] 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 OPTIMISM 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.

Elo-Rd (elotuzumab, lenalidomide and dexamethasone) is another triplet regimen that was studied in patients with 1-3 prior lines of therapy. *As of January 2022, this regimen has received positive PBAC (pharmaceutical benefit advisory committee) recommendations but has yet to be PBS-reimbursed* for the treatment of myeloma patients who have progressed after 1 prior line of therapy. ERd is superior to lenalidomide and dexamethasone (Rd) in the phase III ELOQUENT-2 study [138] with respect to PFS (HR 0.7, p<0.001) and OS (HR0.77, p=0.026). Of note, lenalidomide-refractory patients were excluded from the Eloquent-II study and only approximately 6% of patients in this study were lenalidomide-exposed. Thus, the patient population in this study is not reflective the patient population at relapse in Australia. Nonetheless, ERd could be effective for the subgroup of patients who are not lenalidomide-refractory, particularly, if they were refractory to bortezomib or have peripheral neuropathy making PVd or DVd less ideal.

There are several other effective triplet combinations which are built on the backbone of Rd, but which are *not reimbursed by the Australian PBS*. These include DRd (dartumumab lenalidomide and dexamethasone), KRd (carfilzomib, lenalidomide and dexamethasone) and IRd (ixazomib lenalidomide and dexamethasone). Each of these regimen has been shown to be superior to Rd in patients who have progressed after at least 1 prior line of therapy in the POLLUX (HR 0.37, p<0.0001) [139], ASPIRE (HR 0.69m, p=0.0001) [140], and TOURMALINE-MM1 (HR 0.74, p=0.01) [141], respectively. However, as lenalidomide-refractoriness was an exclusion for enrolment in these studies, their results cannot be confidently extrapolated to the patient-population in Australia with relapsed MM, the majority of whom are refractory to lenalidomide.

Treatment of patients with relapsed and/or refractory MM after more than 3 prior lines of treatment.

In Australia, the options for treatment for patients who have relapsed after 3 prior lines of treatments are limited. Kd or PVd can be used in patients who have not been treated with these respective regimens in earlier lines. Pomalidomide and dexamethasone (Pd) is reimbursed by the PBS for patients who have failed both bortezomib and lenalidomide. A modest median PFS of 4 months can be expected in this group of patients based on the phase III MM003 study [118].

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 12: Recommendation for the treatment of relapsed multiple myeloma:

There is no standard sequence of treatment for patients with relapsed MM. The treatment choice at relapse should be individualised, considering prior therapy and associated toxicity, duration of response to prior therapy, tempo of disease progression, and current physical status. The best treatment option ought to be used early and not saved for the purpose of expanding subsequent treatment option.

- *Common treatment regimens for patient with RRMM are outlined in table 8 (please refer to discussion section 3.4)*
- *Indications to commence treatment at relapse are outlined in table 10*

We recommend enrolment into a clinical trial if one is available as first option.

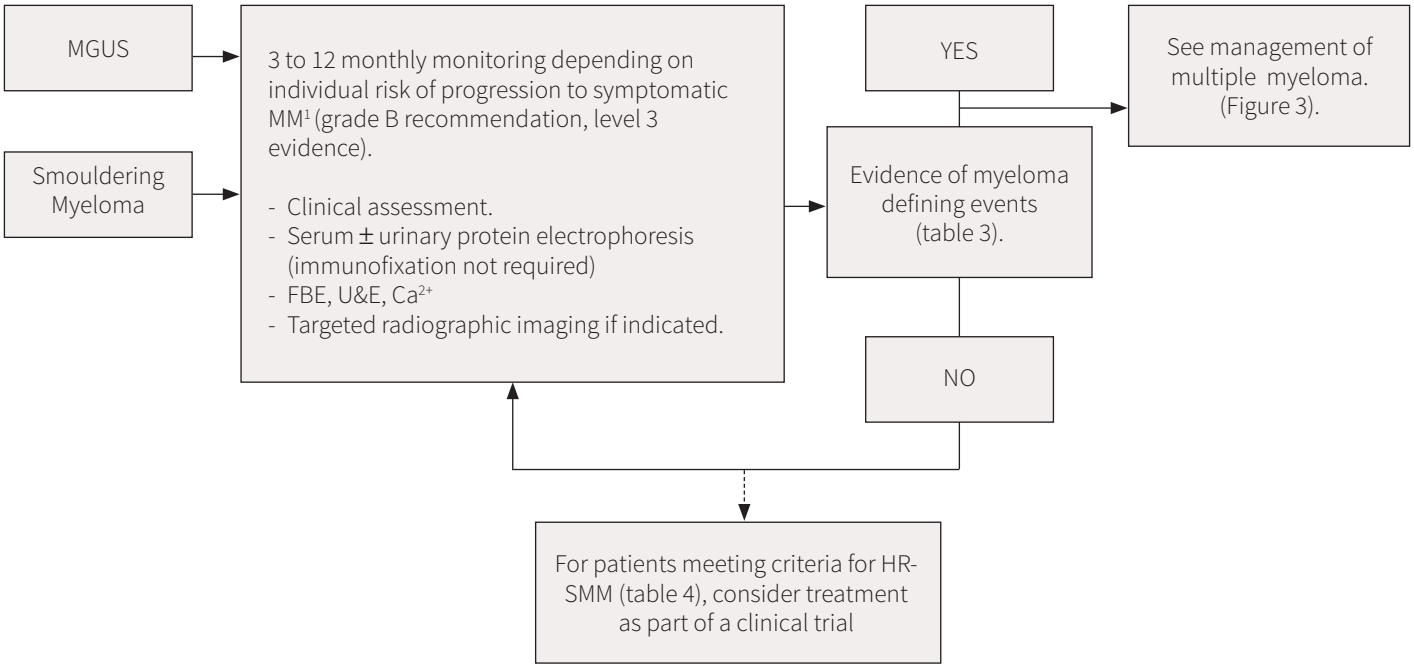
Switch drug class, especially if remission to prior drug was short or patient had concerning associated toxicity

If relapse occurs >12 months following cessation of the last treatment regimen, the same regimen can be re-considered, however, an inferior duration and quality of response is to be expected (Grade C recommendation)

Second ASCT can be considered in a select group of patients who have achieved at least a PR and durable remission (eg. >9 months) to the first ASCT (Grade B recommendation, level 2A evidence).

When all novel agents and different treatment combinations have been exhausted, conventional moderate doses of cyclophosphamide, non-myeloablative doses of melphalan, or low-modest doses of corticosteroids remain viable options, as is palliation in patients who cannot tolerate any further therapy

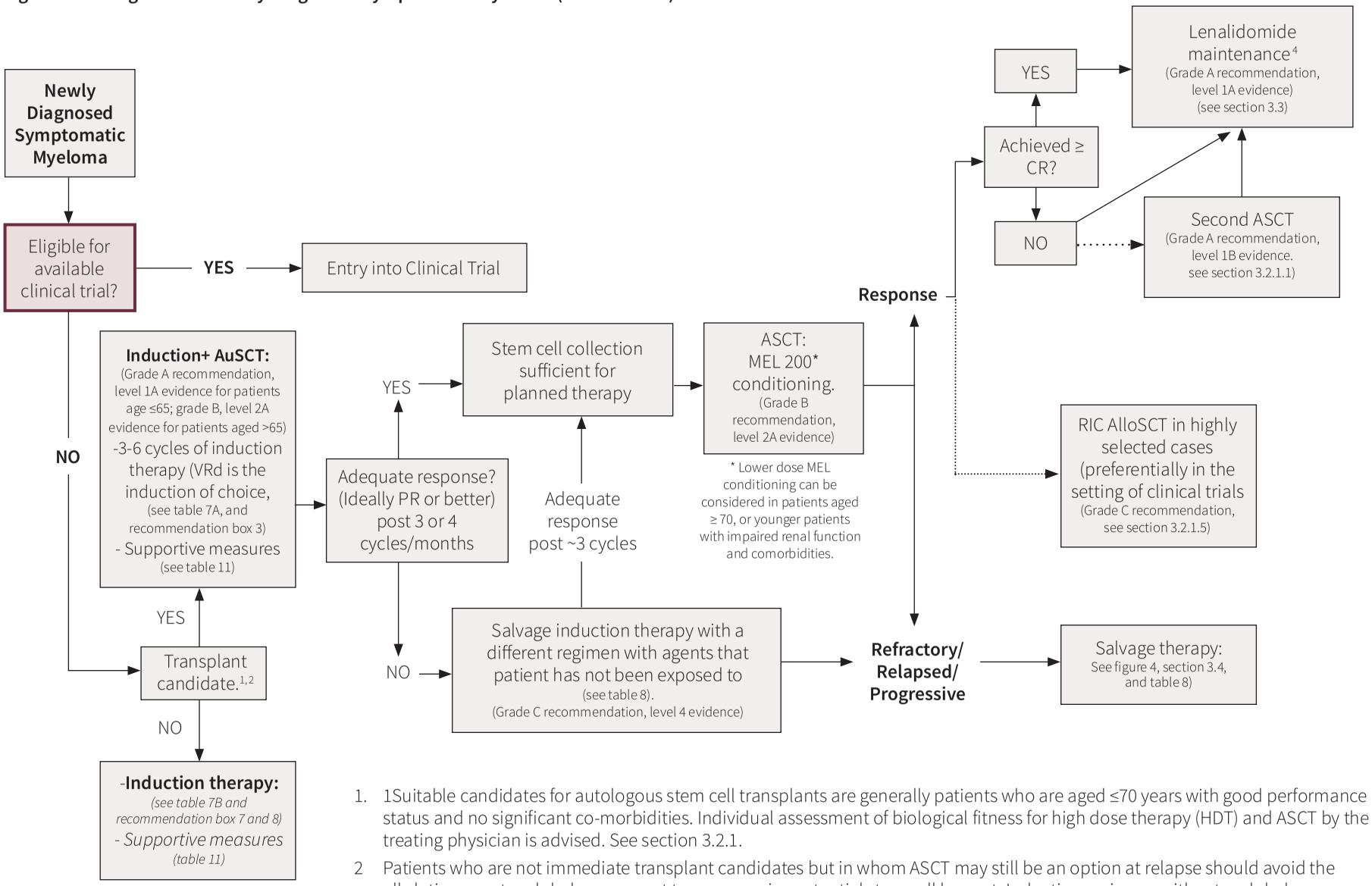
Figure 2: Management of MGUS and Smouldering Myeloma (see section 3.1).



[1]For MGUS:

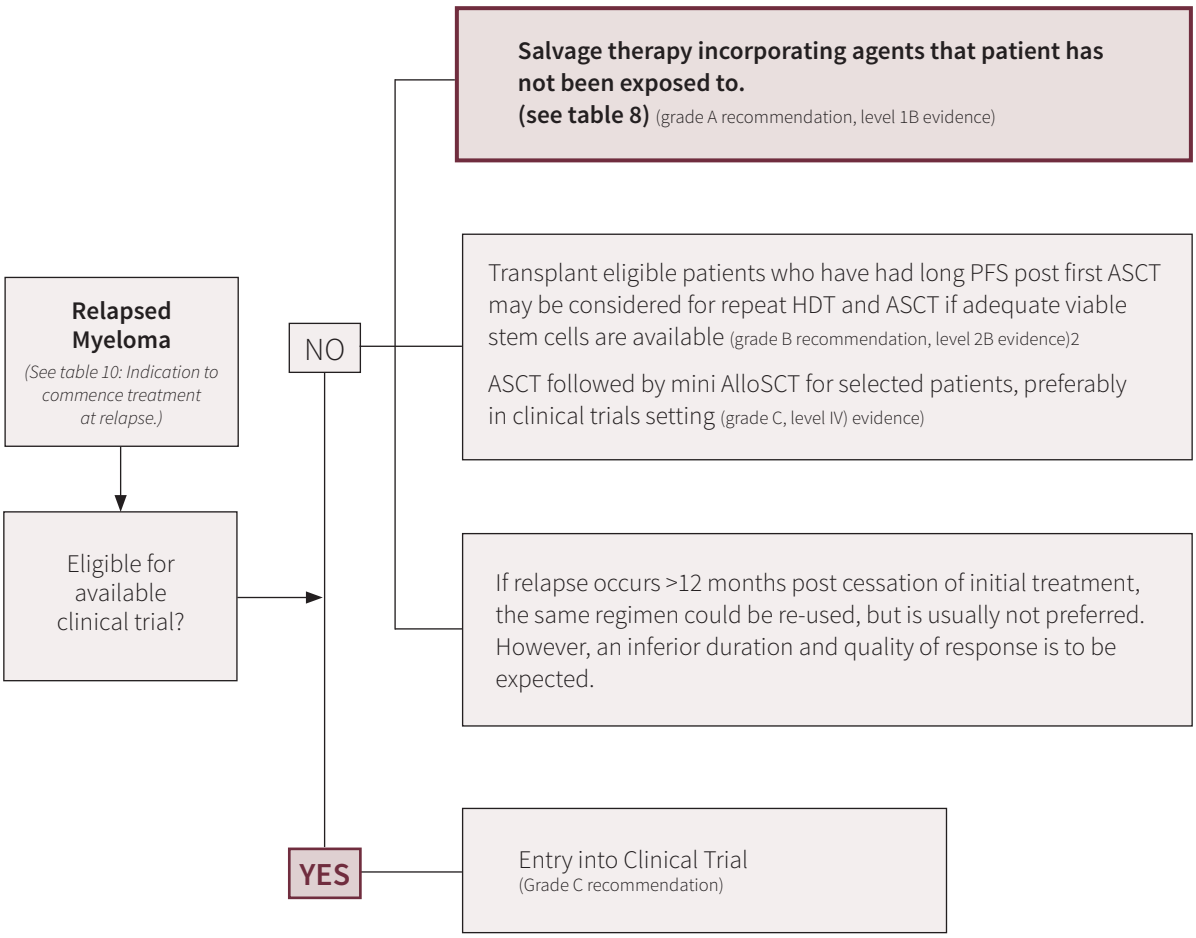
- When serum paraprotein level is ≤15g/l and stable, IgG type, and normal SFLC kappa: lambda ratio, SPEP can be repeated annually.
- When paraprotein value is >15g/l or there is an abnormal SFLC kappa:lambda ratio, a bone marrow aspirate and trephine is considered if paraprotein is rising to assess for evidence of MM. If these results are satisfactory, patients can be followed at 6 monthly intervals for 1 year, then yearly provided the treating physician is contacted upon any clinical changes [11].

Figure 3: Management of Newly Diagnosed Symptomatic Myeloma (see section 3)



1. 1Suitable candidates for autologous stem cell transplants are generally patients who are aged ≤70 years with good performance status and no significant co-morbidities. Individual assessment of biological fitness for high dose therapy (HDT) and ASCT by the treating physician is advised. See section 3.2.1.
2. Patients who are not immediate transplant candidates but in whom ASCT may still be an option at relapse should avoid the alkylating agent melphalan so as not to compromise potential stem cell harvest. Induction regimens without melphalan are outlined in table 7A.

Figure 4: Management of relapsed Myeloma (please see section 3.4)



1. Note: A number of novel agents have been approved by the US FDA (Food Drug Administration) and/or the Australian TGA (Therapeutic Goods Administration) for the treatment of RRMM (see section 4.0) but are currently not reimbursed by the Australian PBS for the treatment of MM. Please refer to section 4.0.
2. Data from the British Blood and Bone Marrow Transplant Registry suggested that a PFS of at least 9 months to the first ASCT is associated with improved survival outcome to a second ASCT in relapsed MM (Cook et al. Biol Blood Marrow Transplant 2011). In the era of novel therapies, most myeloma experts in Australia would consider a second ASCT for salvage therapy upon at least 12-18 months to the first ASCT.

Table 11: Supportive measures.

Localised bony lesions	• Most bone lesions can be treated with chemotherapy and analgesics without the use of radiation therapy. Localised radiation is beneficial in patients with bony pain who have a well-defined focal process. • Patients with lytic lesions in long bones, with threat of fractures should be referred to orthopaedics for prophylactic internal fixation. • Patients with spinal compression fractures and disabling pain may benefit from balloon kyphoplasty[13]; the benefit of vertebroplasty is unclear. • Patients with evidence of spinal cord compression on MRI require surgical intervention, or urgent radiotherapy in combination with corticosteroids if spinal cord compression is due to soft tissue mass arising from vertebrae. • Bisphosphonates: please refer to the Australian guideline for bisphosphonates in the treatment of multiple myeloma[14].
Venothromboembolism (VTE)	• The incidence of VTE is ~1% annually in the general population and is increased by up to 10-30 fold in the presence of malignancy. In MM, this is further increased by the use of thalidomide and lenalidomide. Thalidomide alone does not increase the risk of VTE (incidence ~3-4%), but the risk increases to 14-26% in combination with dexamethasone, and up to approximately 30% when used in combination with chemotherapy, especially anthracyclines. The risk is higher in newly diagnosed patients, and within the first 3 months of therapy. *Lenalidomide, like thalidomide, does not appear to significantly increase the risk of VTE as a single agent.* In combination with dexamethasone or chemotherapy however, VTE risk increases in the order of ~ 14-16%. • VTE prophylaxis is recommended for patients treated with thalidomide, lenalidomide or pomalidomide in combination with high-dose corticosteroids and/or chemotherapy. The choices include aspirin, LMWH (equivalent of enoxaparin 40mg daily) or full dose warfarin (target INR 2-3). The choice is dependent on individual assessment of prothrombotic risks[15]
rEpo	• Recombinant erythropoietin (rEpo) is currently not approved on PBS for use in MM but may be considered in selected patients especially those with renal failure (indication for which it is approved under S100)
IV Ig	Selected patients with recurrent infections (≥2 chest infections per year) and hypogammaglobulinaemia are eligible for IVIg. • Dose: 0.4g/kg every 4 weeks as per CLL. • Please refer to www.nba.gov.au for criteria for the clinical use of intravenous immunoglobulin in Australia.
Infection Prophylaxis.	Pharmaceutical prophylaxis against infection should follow local institutional guidelines. • Valaciclovir, aciclovir or famciclovir prophylaxis against Varicella Zoster reactivation for patients receiving proteasome inhibitors, especially when used in combination with dexamethasone. • Hepatitis B prophylaxis with agents such as entecavir or tenofovir for patients who are tested positive for HBcAb and who are receiving chemotherapy or anti-CD38mAb. All patients who are HBsAg positive should be managed in conjunction with a hepatologist or a specialist experienced in the management of chronic hepatitis B. • Trimethoprim-Sulfamethoxazole prophylaxis against Pneumocystis Jiroveci in patients who are on high dose corticosteroids that is equivalent to at least 20mg of prednisolone daily for at least 4 weeks. Dapsone, Pentamidine or Atovaquone are possible second line prophylactic agents if Trimethoprim-Sulfamethoxazole is contraindicated. • Patients should be vaccinated against hepatitis B, pneumococcus, influenza and other pathogens deemed necessary because of epidemiologic prevalence. Live vaccines should be avoided. Non-immune close contacts of patients should also be vaccinated[16]
Other prophylaxis	• Proton pump inhibitor or histamine H2-receptor antagonist is recommended in patients receiving ongoing corticosteroids

4 AGENTS NOT CURRENTLY REIMBURSED BY THE AUSTRALIAN PBS AND OTHER EMERGING NOVEL THERAPEUTICS

Treatment options for people with MM continues to expand, with a surge of novel effective agents reaching late clinical development if not the clinics in recent years. The main issue for Australia, as is the case with many countries around the world is affordable drug access of novel agents. The Australian national health care system provides subsidised access to health care services through Medicare and prescription drugs through the Pharmaceutical Benefits Scheme (PBS). The regulatory approval of anti-myeloma therapeutics by the Australian Therapeutics Good Administration (TGA), in turn paves way for consideration for PBS subsidisation of a novel drug, but usually lags that of the US Food and Drug Administration (FDA) which is the US regulatory equivalent of the Australian TGA. It is important to note that the funding system of drugs is highly different in Australia, being nationalised, compared with jurisdictions such as the US which is largely insurance-based.

Below is a non-exhaustive overview of the most promising agents that may or may not be TGA approved but are not PBS reimbursed. Amongst these, those which are TGA approved for the treatment of MM are the second-generation PI ixazomib, the monoclonal antibodies elotuzumab and isatuximab, and the histone deacetylase inhibitor (HDACi) panobinostat. The others are in ongoing clinical trials and include novel immune therapies such as chimeric antigen receptor – T cells (CAR-T cells), T cell engagers (TCEs), antibody drug conjugates (ADCs) as well as small molecules including the BH3-mimetic, venetoclax, the selective inhibitor of nuclear export (SINE), Selinexor.

Second Generation Proteasome inhibitors (PI):

Ixazomib (Ninlaro®, Takeda) is a second generation PI that is given orally. *Ixazomib in combination with lenalidomide and dexamethasone (IRd)* is TGA approved for the treatment of patients with RRMM who have had at least 1 prior line of treatment, based on results of the TOURMALINE-1 study that demonstrated superiority of IRd compared to Rd with respect to PFS (HR 0.74, p=0.01) [141]. In the upfront setting, combination ILd has been shown to be effective in a phase II study[142].

Monoclonal antibodies (mAb):

Daratumumab (Darazalex®; Janssen) is the first in class human IgG1K against CD38. Daratumumab is only reimbursed by the Australian PBS in combination with bortezomib and dexamethasone (Dara-Vd) for second-line treatment of patients with RRMM.

Daratumumab in combination with lenalidomide and dexamethasone (DRd) is TGA-approved for patients who have had at least one prior line of treatment, based on results from the phase III POLLUX study [139] in which DRd was superior to Rd with respect to PFS (HR 0.37, (p<0.0001).

Daratumumab monotherapy is also TGA-approved for patients who have had at least three prior lines of therapy including PI and IMID or who are refractory to both, based on a study of heavily pretreated patients who were mostly (86%) refractory to both IMIDs and PI showing an ORR 31% (≥VGPR 13%) and PFS 19.9 months [143].

Daratumumab in combination with each of the backbone bortezomib, melphalan and prednisolone (DVMP) or lenalidomide and dexamethasone (DRd) are TGA-approved for upfront treatment in TIE patients. The approvals were based on results from two large phase III randomised study, the ALCYONE[94] and MAIA[95] study demonstrating that DVMP and DRd, respectively, were superior to their control backbone with respect to PFS (HR 0.5 for Dara-VMP vs. VMP, p<0.001; HR 0.55 for Dara-Rd vs. Rd, p<0.0001, respectively).

Isatuximab (Sarclista®; Sanofi) 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-MM[144] and IKEMA[145] studies, respectively.

Elotuzumab (Empliciti®, Bristol-Myers Squibb) is a humanised mAb to SLAMF7 that is highly specific to plasma cells although it may also be expressed on NK cells. *Elotuzumab in combination with lenalidomide and dexamethasone (ERd)* is TGA-registered for the treatment of patients with myeloma who have had at least 1 prior line of treatment, based on results of the phase III ELOQUENT-2 study that demonstrated superiority of ERd compared to Rd respect to PFS (HR 0.7, p<0.001) and OS (HR0.77, p=0.026) [138]. Elo-Rd is now reimbursed on the Australian PBS (Table 8).

Histone deacetylase inhibitors (HDACi):

Panabinostat (Farydak®; Novartis) is a pan-histone deacetylase inhibitor (HDACi) that works via epigenetic activity targeting histones, but also acetylate non-histone proteins relevant to tumour progression[146]. *Panobinostat in combination with bortezomib and dexamethasone (FVd)* is TGA approved for the treatment of RRMM in patients who have had at least 2 prior therapies, based on results of the phase III PANORAMA-1 study that demonstrated that FVd improved PFS by 4 months (p<0.001) compared to Vd[147]. The use of bortezomib subcutaneously improved tolerability, and Panobinostat 20mg three times per week seem to result in the deepest and most durable response in the follow up PANORAMA-3 study[148].

Small Molecules:

Selinexor (Xpovio®; Karyopharm) is an oral first in class selective inhibitor of nuclear export (SINE) which specifically blocks exportin-1 (XPO1), and ultimately results in both the nuclear retention and activation of tumour suppressor genes as well as translational suppression of oncogenes. Based on the phase 2b STORM study, selinexor was the first agent to have demonstrated clinically meaningful activity (≥PR 26.2%) in a group of penta refractory patients with otherwise dismal prognosis (expect median OS 1.3-3.5m) and no established beneficial therapies at current time[149]. In patients with 1 to 3 prior lines of treatment, selinexor in combination with bortezomib and dexamethasone (XVd) is superior to Vd with respect to PFS (HR 0.7, p=0.0075) in the phase III BOSTON study[150]. Selinexor Dexamethazone (Xd) is now reimbursed on the Australian PBS (Table 8).

Venetoclax (Venclexta®, Abbvie), a BCL-2 inhibitor, is particularly effective for patients with t(11;14) with high Bcl-2 expression, inducing an ORR of 86% in this population in a phase I dose escalation study[151]. In the phase III BELINI study[152], combination Venetoclax, bortezomib and dexamethasone (VenVd) was superior to Vd with respect to PFS (HR 0.63, p=0.01), however, there was increased mortality in the Venetoclax arm due to increased rate of infections. For the subset of patients with t(11;14) or high BCL-2, the benefit risk profile was favourable, with a significant improvement in PFS from VenVd compared to Vd (HR 0.11 (p=0.02) for t(11;14) subgroup; HR 0.34, p=0.01 for the high BCL2 subgroup). Ventoclax is in ongoing investigations with different combinations. As of January 2022, venetoclax is not TGA-registered for the treatment of MM, but may be accessed for compassionate use through Abbvie for patients with t(11;14) who have exhausted treatment options.

Immune therapies:

In addition to mAbs, other immune therapies that are making rapid headways in the treatment of MM include chimeric antigen receptor T cells (CAR-T), bispecific antibodies and antibody drug conjugates (ADCs). *These agents are not TGA-registered and are not PBS reimbursed for the treatment of MM as of January 2022.*

CAR-T cells are autologous T cells that are genetically engineered ex-vivo, to express an artificial receptor capable of recognising the antigen of interest on malignant cells. Several products exists for MM, the forerunners of which are **idecabtagene vicleucel** (**ide-cel; Abecma®,** BMS) **and ciltacabtagene autoleucel** (**Cilta-cel;** Janssen). Ide-cel is FDA-approved in the US for the treatment of patients with RRMM who are triple-class exposed (ie. prior exposure to IMID, PI and anti-CD38 mAb) after 4 lines of therapies, based on results of the phase II KarMMA Study that demonstrated deep (sCR 28%) and durable responses (median duration of response 11 months) in heavily pre-treated patients, 88% and 85% of whom have had at least 4 prior lines of therapy and were triple class refractory, respectively. Cilta-cel is equally impressive with a reported ORR of 98% (80% sCR) and median duration of response of 21.8 months in a similarly heavily pre-treated group of patients[153].

Unlike CAR-T cells, **bispecific antibodies** have the benefit of being an "off the shelf product", with promising efficacy, based on preliminary results on early phase studies. These are antibody-based molecules designed to bind both target antigen on myeloma cells and cytotoxic immune effector cells (T cells or NK cells). The products leading in clinical development are bispecific T-cell engaging antibodies which include those targeting BCMA on myeloma cells (eg. **Teclistamab, Elranatamab and AMG 701**), FcRH5 (eg. **Cevostamab**), and GPR5CD (**Talquetamab**).

Currently, the only ADC that has reached the clinic for the treatment of MM is **belantamab mafodotin** (**Blenrep®,** GlaxoSmithKline); this is humanised IgG1 anti-BCMA antibody conjugated to the microtubule disrupting agent monomethyl auristatin-F. Belantamab Mafodotin is FDA-approved in the US for the treatment of patients with RRMM after 4 prior lines of treatment based on results of the phase II DREAMM-2 study that demonstrated an ORR of 31% at the recommended 2.5mg/kg dose every 3 weeks, and a DOR that was not reached at the 6-month analysis. *As of January 2022, belalantamab mafodotin may be accessed on a compassionate program through GlaxoSmithKline for eligible patients.*

Alkylating Agents:

Bendamustine (**Treanda®,** Janssen-Cilag) 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 alkylators[154]. In phase I and II trials, bendamustine was efficacious as monotherapy, and in combination with thalidomide, lenalidomide or bortezomib[155]. 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 treatment[156].

5 CONCLUDING REMARKS

The treatment for multiple myeloma has become more complex as the therapeutic landscape expands. What is considered as standard therapy will continue to change as trial data mature with respect to newer-therapeutic agents. It is important to note that the standard of care in Australia may differ from that in the US and Europe, and is based on what is reimbursed by the Australian PBS, which in turn, is subjected to rigorous evidence-based and cost analysis assessment. At present, MM remains an incurable disease. It is anticipated that survival for patients with MM will continue to improve as more effective novel agents are approved and made available for use in the clinic. The above treatment guideline from the Australian Medical Scientific Advisory Group (MSAG) to Myeloma Australia is based on current published data, local clinical experience and PBS-approved therapies. We believe that a national consensus of treatment algorithm for MM will not only improve patterns of care nationally, but will also establish a foundation for future clinical studies that are locally-relevant.

The above guideline is based on up-to-date information as of June 2022. Some aspect of this guideline may change in the future depending on emerging data from clinical studies. This guideline is due for review in February 2024.

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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